

EPA Registration Number 264-1056 Part 1



264-1056



009270626

el

Bayer CropScience



March 20, 2008

Document Processing Desk
Office of Pesticide Programs (7505P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, Virginia 22202-4501

ATTENTION: Kable Bo Davis (RD, Insecticide-Rodenticide Branch))

**Re: Final Printed Label for Poncho Beta
(EPA Reg. No. 264-1056)**

Dear Mr. Davis,

In compliance with your March 7, 2008 approval letter, we are herein submitting one copy of the final printed label for Poncho Beta dated March 7, 2008 for your record. All of the required revisions in the March 7, 2008 Notice of Registration are incorporated in this labeling. With your agreement today, we use "bagging and sewing/boxing" instead of "bagging and sewing" in the revised PPE section since sugar beet treaters put treated seeds in boxes instead of in bags.

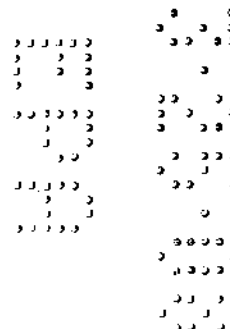
Bayer CropScience
2 T.W. Alexander Drive
P. O. Box 12014
Research Triangle Park,
NC 27709
Tel: 919 549-2000

Please let me know at jamin.huang@bayercropscience.com or at 919-549-2634 if you have any questions regarding this submission.

Sincerely,

Jamin Huang, Ph.D.
Product Registration Manager

Attachment



PONCHO BETA

NOT REVIEWED
In Accordance with PR Notice 82-2
Based on Draft Labeling Dated

Poncho Beta is a systemic insecticide seed treatment for use on sugar beet for the control of certain insect pests.

All seed treated with this product must be conspicuously colored at the time of treatment. MAR - 7 2008

ACTIVE INGREDIENTS:

Clothianidin..... 34.3%
beta-Cyfluthrin..... 4.6%

INERT INGREDIENTS:61.1%

TOTAL:100.0%

Contains 3.33 lb active per gallon (400 grams per liter) clothianidin and 0.44 lb active per gallon (53.3 grams per liter) beta-cyfluthrin

E.P.A. Reg. No. 264-1056

E.P.A. Est. No.

KEEP OUT OF REACH OF CHILDREN CAUTION

Si usted no entiende la etiqueta, busque a alguien para que se la explique a usted en detalle.

(If you do not understand the label, find someone to explain it to you in detail.)

For MEDICAL And TRANSPORTATION Emergencies ONLY Call 24 Hours A Day 1-800-334-7577

For PRODUCT USE Information Call 1-866-99BAYER (1-866-992-2937)

FIRST AID

IF ON SKIN OR CLOTHING:	<ul style="list-style-type: none">• Take off contaminated clothing.• Rinse skin immediately with plenty of water for 15-20 minutes.• Call a poison control center or doctor for treatment advice.
IF SWALLOWED:	<ul style="list-style-type: none">• Immediately call a poison control center or doctor for treatment advice.• Have person sip a glass of water if able to swallow.• Do not induce vomiting unless told to do so by a poison control center or doctor.• Do not give anything by mouth to an unconscious person.
For <u>MEDICAL</u> Emergencies Call 24 Hours A Day 1-800-334-7577. Have the product container or label with you when calling a poison control center or doctor or going for treatment.	

NOTE TO PHYSICIAN: No specific antidote is available. Treat the patient symptomatically.

PRECAUTIONARY STATEMENTS

HAZARD TO HUMANS AND DOMESTIC ANIMALS

CAUTION

Harmful if absorbed through the skin. Harmful if swallowed. Avoid contact with skin or clothing. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Wear long-sleeved shirt and long pants, sock, shoes, and gloves. Remove and wash contaminated clothing before reuse. Wear appropriate protective clothing.

PERSONAL PROTECTIVE EQUIPMENT (PPE)

Some materials that are chemical-resistant to this product are listed below. If you want more options, follow the instructions for category C on an EPA chemical resistance category selection chart.

Workers involved with treating the seed (e.g. connecting and disconnecting hoses and transfer pumps, mixing, equipment calibration, etc.) and others exposed to the concentrate, and cleaners/repairers of seed treatment equipment must wear a long-sleeved shirt and long pants, chemical-resistant gloves (such as nitrile, butyl, neoprene, barrier laminate, polyvinyl chloride or Viton), shoes plus socks and a dust/mist filtering respirator (MSHA/NIOSH approval number prefix TC-21C).

Baggers and bag sewers must wear a long-sleeved shirt and long pants, shoes plus socks, and a dust/mist filtering respirator, (MSHA/NIOSH approval number prefix TC-21C).

Follow manufacturer's instructions for cleaning/maintaining PPE. If no instructions for washables, use detergent and hot water. Keep and wash PPE separately from other laundry.

NOTE: For all workers that handle all seed treatment steps like loading, treating, bagging and sewing/boxing, alone on a daily basis, the following additional PPE must be worn:

- Double layer clothing

- A respirator with an organic-vapor removing cartridge with a prefilter approved for pesticides (MSHA/NIOSH approval number prefix TC-23C), or a canister approved for pesticides (MSHA/NIOSH approval number prefix TC-14-G), or a NIOSH-approved respirator with an organic vapor (OV) cartridge or canister with any N, R or P or HE prefilter.

USER SAFETY RECOMMENDATIONS

Users should: Wash hands before eating, drinking, chewing gum, using tobacco or using the toilet. Remove clothing immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing. Remove Personal Protective Equipment immediately after handling this product. Wash the outside of gloves before removing. As soon as possible, wash thoroughly and change into clean clothing.

ENVIRONMENTAL HAZARDS

This product is toxic to aquatic invertebrates. Contain any product spills or equipment leaks and dispose of wastes according to disposal instructions on this label. Do not contaminate water when disposing of equipment washwaters.

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.
Read entire label before using this product.

Intended for use by commercial treaters. Not for use in agricultural establishments in hopper-box, slurry-box, or similar on farm seed treatment applicators used at planting. This product is to be used in commercial liquid or slurry treaters. Mix thoroughly before use or use entire container at one time.

All seed treated with this product must be conspicuously colored at the time of treatment. This product contains no colorant. An appropriate colorant must be added when this product is applied to seed to distinguish and prevent subsequent inadvertent use as a food for man or feed for animals. Regulations pertaining to coloration of treated seed enforced by 40 CFR 153.155 must be strictly adhered to when using this product.

STORAGE AND DISPOSAL

STORAGE

Do not contaminate water, food or feed by storage or disposal. Store in a cool, dry secured storage area.

PESTICIDE DISPOSAL

Wastes resulting from the use of this product may be disposed of on site or at an approved waste disposal facility.

CONTAINER DISPOSAL

Non-refillable container. Do not reuse or refill this container. Offer for recycling, if available. Triple rinse container (or equivalent) promptly after emptying. Triple rinse as follows: Empty the remaining contents into application equipment or a mix tank. Fill the container 1/4 full with water. Replace and tighten closure. Tip container on its side and roll it back and forth, ensuring at least one complete revolution, for 30 seconds. Stand the container on its end and tip it back and forth several times. Empty the rinsate into application equipment or a mix tank or store rinsate for later use or disposal. Repeat this procedure two more times. Then offer for recycling or reconditioning or puncture and dispose of in a sanitary landfill or incineration, or if allowed by state and local authorities, by burning. If burned, stay out of smoke.

FOR EARLY SEASON PROTECTION AGAINST CERTAIN INSECTS OF SUGAR BEET:

To provide early season protection of seeds and seedlings against injury by wireworm, cutworms, sugar beet leafhopper (including to reduce potential for spread of beet curly top virus due to the leafhopper vector), sugar beet leafminer, sugar beet root maggot, flea beetle, black bean aphid, and garden springtail, apply as a commercial seed treatment at a rate of 5.07 fluid ounces per unit of seed (a unit is 100,000 seed). Apply Poncho Beta to seed with a coating system that gives a minimum build-up of approximately 30% weight gain.

ROTATIONAL CROPS:

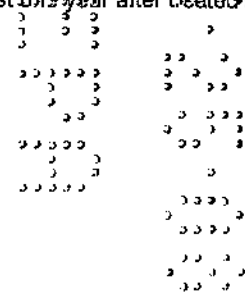
Treated areas may be replanted with any crop specified on both clothianidin and beta-cyfluthrin labels, or any crop for which a tolerance exists for both active ingredients, as soon as practical following the last application. Areas planted with treated seed may be replanted immediately with cotton, corn, sorghum, rapeseed and canola. These areas may also be replanted after 30 days with cereal grains, soybeans, dried beans and dried peas. Do not plant any other crop in the treated area for at least one year after treated seeds are planted.

LABELING OF TREATED SEED

Seed commercially treated with Poncho Beta must be labeled in compliance with the *Federal Seed Act*.

Seed commercially treated with Poncho Beta must be labeled or tagged as follows:

- This seed has been treated with Poncho Beta, which contains clothianidin and beta-cyfluthrin.
- Do not use treated seed for food, feed or oil processing.



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- Store away from feeds and foodstuffs.
- Wear long-sleeved shirt, long pants and waterproof gloves when handling treated seed.
- Dispose of all excess treated seed. Left over treated seed may be double own around the headland or buried away from water sources in accordance with local requirements. Do not contaminate water bodies when disposing of planting equipment washwaters.
- Dispose of seed packaging in accordance with local requirements.
- Treated seeds exposed on soil surface may be hazardous to wildlife. Cover or collect treated seeds spilled during loading.
- Treated areas may be replanted with any crop specified on both clothianidin and cyfluthrin labels, or any crop for which a tolerance exists for both active ingredients, as soon as practical following the last application. Areas planted with treated seed may be replanted immediately with cotton, corn, sorghum, rapeseed and canola. These areas may also be replanted after 30 days with cereal grains, soybeans, dried beans dried peas. Do not plant any other crop in the treated area for at least one year after treated seeds are planted.

All seed treated with this product must be conspicuously colored at the time of treatment. This product contains no colorant. An appropriate colorant must be added when this product is applied to seed to distinguish and prevent subsequent inadvertent use as a food for man or feed for animals. Regulations pertaining to coloration of treated seed enforced by 40 CFR 153.155 must be strictly adhered to when using this product.

IMPORTANT: READ BEFORE USE

Read the entire Directions for Use, Conditions, Disclaimer of Warranties and Limitations of Liability before using this product. If terms are not acceptable, return the unopened product container at once.

By using this product, user or buyer accepts the following Conditions, disclaimer of Warranties and Limitations of Liability.

Treatment of highly mechanically damaged seed, or seed of known low vigor and poor quality, may result in reduced germination and/or reduction of seed and seedling vigor. Treat and conduct germination tests on a small portion of seed before committing the total seed lot to a selected chemical treatment. Due to seed quality conditions beyond the control of Bayer CropScience, no claims are made to guarantee germination of carry-over seed.

CONDITIONS: The directions for use of this product are believed to be adequate and must be followed carefully. However, it is impossible to eliminate all risks associated with the use of this product. Crop injury, ineffectiveness or other unintended consequences may result because of such factors as weather conditions, presence of other materials, or the manner of use or application, all of which are beyond the control of Bayer CropScience. All such risks shall be assumed by the user or buyer.

DISCLAIMER OF WARRANTIES: TO THE EXTENT CONSISTENT WITH APPLICABLE LAW, BAYER CROPSCIENCE MAKES NO OTHER WARRANTIES, EXPRESS OR IMPLIED, OF MERCHANTABILITY OR OF FITNESS FOR A PARTICULAR PURPOSE OR OTHERWISE, THAT EXTEND BEYOND THE STATEMENTS MADE ON THIS LABEL. No agent of Bayer CropScience is authorized to make any warranties beyond those contained herein or to modify the warranties contained herein. TO THE EXTENT CONSISTENT WITH APPLICABLE LAW, BAYER CROPSCIENCE DISCLAIMS ANY LIABILITY WHATSOEVER FOR SPECIAL, INCIDENTAL OR CONSEQUENTIAL DAMAGES RESULTING FROM THE USE OR HANDLING OF THIS PRODUCT.

LIMITATIONS OF LIABILITY: TO THE EXTENT CONSISTENT WITH APPLICABLE LAW, THE EXCLUSIVE REMEDY OF THE USER OR BUYER FOR ANY AND ALL LOSSES, INJURIES OR DAMAGES RESULTING FROM THE USE OR HANDLING OF THIS PRODUCT, WHETHER IN CONTRACT, WARRANTY, TORT, NEGLIGENCE, STRICT LIABILITY OR OTHERWISE, SHALL NOT EXCEED THE PURCHASE PRICE PAID, OR AT BAYER CROPSCIENCE'S ELECTION, THE REPLACEMENT OF PRODUCT.

NOTICE TO BUYER

Purchase of this material does not confer any rights under patents governing this product or the use thereof in countries outside of the United States.

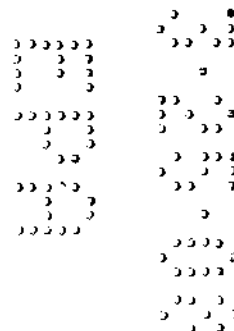
NET CONTENTS:

Produced for



Bayer CropScience

Bayer CropScience LP
P.O. Box 12014, 2 T.W. Alexander Drive
Research Triangle Park, North Carolina 27709
1-866-99BAYER (1-866-992-2937)
<http://www.bayercropscienceus.com>





U.S. ENVIRONMENTAL PROTECTION AGENCY

Office of Pesticide Programs
Registration Division (7505C)
1200 Pennsylvania Ave., N.W.
Washington, D.C. 20460

EPA Reg. Number:

264-1056

Date of Issuance:

MAR 7 2008

NOTICE OF PESTICIDE:

☒ Registration
☐ Reregistration

(under FIFRA, as amended)

Term of Issuance:

Conditional

Name of Pesticide Product:

Poncho Beta

Name and Address of Registrant (include ZIP Code):

Bayer CropScience
2 T.W. Alexander Drive
Research Triangle Park, NC 27709

Note: Changes in labeling differing in substance from that accepted in connection with this registration must be submitted to and accepted by the Registration Division prior to use of the label in commerce. In any correspondence on this product always refer to the above EPA registration number.

On the basis of information furnished by the registrant, the above named pesticide is hereby registered/reregistered under the Federal Insecticide, Fungicide and Rodenticide Act.

Registration is in no way to be construed as an endorsement or recommendation of this product by the Agency. In order to protect health and the environment, the Administrator, on his motion, may at any time suspend or cancel the registration of a pesticide in accordance with the Act. The acceptance of any name in connection with the registration of a product under this Act is not to be construed as giving the registrant a right to exclusive use of the name or to its use if it has been covered by others.

This product is conditionally registered in accordance with FIFRA section 3(c)(7)(A) provided that you:

1. Submit and/or cite all data required for registration/reregistration of your product when the Agency requires all registrants of similar products to submit such data.
2. Make the following label changes before you release the product for shipment:
 - a. Revise the EPA Registration Number to read, "EPA Reg. No. 264-1056".
 - b. Within the **DIRECTIONS FOR USE** section of the label, revise "For use by commercial treaters only." to read "Intended for use by commercial treaters."
 - c. Within the ingredient statement (page one) revise "ACTIVE INGREDIENT" to read "ACTIVE INGREDIENTS."

Signature of Approving Official:

Kable Bo Davis, Entomologist
Insecticide-Rodenticide Branch, Registration Division (7505P)

Date:

MAR 7 2008

- d. Within the **PERSONAL PROTECTIVE EQUIPEMENT (PPE)** section of the label, additional language must be included stating that for those workers that handle all seed treatment steps like loading, treating, bagging and sewing, alone on a daily basis, the following additional PPE must be worn:
 - double layer clothing
 - a respirator with an organic-vapor removing cartridge with a prefilter approved for pesticides (MSHA/NIOSH approval number prefix TC-23C), or a canister approved for pesticides (MSHA/NIOSH approval number prefix TC-14-G), or a NIOSH-approved respirator with an organic vapor (OV) cartridge or canister with any N,R or P or HE prefilter
3. The data requirement for a developmental immunotoxicity study has not been satisfied, and must be submitted upon completion.
4. Per request of the Clothianidin: Human Health Risk Assessment for Proposed Use on Sugar Beet memorandum dated October 16, 2007, the data cited to support the stability of TMG in frozen sugar beet leaves, and potato tubers, flakes and chips must be submitted for evaluation.
5. The data requirements for storage stability (830-6317) and corrosion characteristics (830-6320) have not been satisfied, and must be submitted within eighteen months of the date of this letter.
6. Submit one copy of the revised printed label for the record before you release the product for shipment.

If these conditions are not complied with, the registration will be subject to cancellation in accordance with FIFRA section 6(e). Your release for shipment of the product constitutes acceptance of these conditions.

A stamped copy of the label is enclosed for your records.

Kable Bo Davis
Entomologist
Insecticide-Rodenticide Branch
Registration Division (7505P)

Enclosure

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PONCHO BETA

Poncho Beta is a systemic insecticide seed treatment for use on sugar beet for the control of certain insect pests.
All seed treated with this product must be conspicuously colored at the time of treatment.

ACTIVE INGREDIENT:

Clothianidin..... 34.3%
beta-Cyfluthrin..... 4.6%

INERT INGREDIENTS:61.1%

TOTAL:100.0%

Contains 3.33 lb active per gallon (400 grams per liter) clothianidin and 0.44 lb active per gallon (53.3 grams per liter) beta-cyfluthrin

E.P.A. Reg. No. 264-XXX

E.P.A. Est. No.

KEEP OUT OF REACH OF CHILDREN CAUTION

Si usted no entiende la etiqueta, busque a alguien para que se la explique a usted en detalle.
(If you do not understand the label, find someone to explain it to you in detail.)

For MEDICAL And TRANSPORTATION Emergencies ONLY Call 24 Hours A Day 1-800-334-7577
For PRODUCT USE Information Call 1-866-99BAYER (1-866-992-2937)

FIRST AID

IF ON SKIN OR CLOTHING:	<ul style="list-style-type: none">• Take off contaminated clothing.• Rinse skin immediately with plenty of water for 15-20 minutes.• Call a poison control center or doctor for treatment advice.
IF SWALLOWED:	<ul style="list-style-type: none">• Immediately call a poison control center or doctor for treatment advice.• Have person sip a glass of water if able to swallow.• Do not induce vomiting unless told to do so by a poison control center or doctor.• Do not give anything by mouth to an unconscious person.
For MEDICAL Emergencies Call 24 Hours A Day 1-800-334-7577. Have the product container or label with you when calling a poison control center or doctor or going for treatment.	

NOTE TO PHYSICIAN: No specific antidote is available. Treat the patient symptomatically.

PRECAUTIONARY STATEMENTS

HAZARD TO HUMANS AND DOMESTIC ANIMALS

CAUTION

Harmful if absorbed through the skin. Harmful if swallowed. Avoid contact with skin or clothing. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Wear long-sleeved shirt and long pants, sock, shoes, and gloves. Remove and wash contaminated clothing before reuse. Wear appropriate protective clothing.

PERSONAL PROTECTIVE EQUIPMENT (PPE)

Some materials that are chemical-resistant to this product are listed below. If you want more options, follow the instructions for category C on an EPA chemical resistance category selection chart.

Workers involved with treating the seed (e.g. connecting and disconnecting hoses and transfer pumps, mixing, equipment calibration, etc.) and others exposed to the concentrate, and cleaners/repairers of seed treatment equipment must wear a long-sleeved shirt and long pants, chemical-resistant gloves (such as nitrile, butyl, neoprene, barrier laminate, polyvinyl chloride or Viton), shoes plus socks and a dust/mist filtering respirator (MSHA/NIOSH approval number prefix TC-21C).

Baggers and bag sewers must wear a long-sleeved shirt and long pants, shoes plus socks, and a dust/mist filtering respirator (MSHA/NIOSH approval number prefix TC-21C).

Follow manufacturer's instructions for cleaning/maintaining PPE. If no instructions for washables, use detergent and hot water. Keep and wash PPE separately from other laundry.

**ACCEPTED
with COMMENTS
In EPA Letter Dated:**

MAR 7 2008

Under the Federal Insecticide,
Fungicide, and Rodenticide Act,
as amended, for the pesticide
registered under EPA Reg. No. 1 8
264-105-6

USER SAFETY RECOMMENDATIONS

Users should: Wash hands before eating, drinking, chewing gum, using tobacco or using the toilet. Remove clothing immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing. Remove Personal Protective Equipment immediately after handling this product. Wash the outside of gloves before removing. As soon as possible, wash thoroughly and change into clean clothing.

ENVIRONMENTAL HAZARDS

This product is toxic to aquatic invertebrates. Contain any product spills or equipment leaks and dispose of wastes according to disposal instructions on this label. Do not contaminate water when disposing of equipment washwaters.

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

Read entire label before using this product.

For use by commercial treaters only. Not for use in agricultural establishments in hopper-box, slurry-box, or similar on farm seed treatment applicators used at planting. This product is to be used in commercial liquid or slurry treaters. Mix thoroughly before use or use entire container at one time.

All seed treated with this product must be conspicuously colored at the time of treatment. This product contains no colorant. An appropriate colorant must be added when this product is applied to seed to distinguish and prevent subsequent inadvertent use as a food for man or feed for animals. Regulations pertaining to coloration of treated seed enforced by 40 CFR 153.155 must be strictly adhered to when using this product.

STORAGE AND DISPOSAL

STORAGE

Do not contaminate water, food or feed by storage or disposal. Store in a cool, dry secured storage area.

PESTICIDE DISPOSAL

Wastes resulting from the use of this product may be disposed of on site or at an approved waste disposal facility.

CONTAINER DISPOSAL

Non-refillable container. Do not reuse or refill this container. Offer for recycling, if available. Triple rinse container (or equivalent) promptly after emptying. Triple rinse as follows: Empty the remaining contents into application equipment or a mix tank. Fill the container 1/4 full with water. Replace and tighten closure. Tip container on its side and roll it back and forth, ensuring at least one complete revolution, for 30 seconds. Stand the container on its end and tip it back and forth several times. Empty the rinsate into application equipment or a mix tank or store rinsate for later use or disposal. Repeat this procedure two more times. Then offer for recycling or reconditioning or puncture and dispose of in a sanitary landfill or incineration, or if allowed by state and local authorities, by burning. If burned, stay out of smoke.

FOR EARLY SEASON PROTECTION AGAINST CERTAIN INSECTS OF SUGAR BEET:

To provide early season protection of seeds and seedlings against injury by wireworm, cutworms, sugar beet leafhopper (including to reduce potential for spread of beet curly top virus due to the leafhopper vector), sugar beet leafminer, sugar beet root maggot, flea beetle, black bean aphid, and garden springtail, apply as a commercial seed treatment at a rate of 5.07 fluid ounces per unit of seed (a unit is 100,000 seed). Apply Poncho Beta to seed with a coating system that gives a minimum build-up of approximately 30% weight gain.

ROTATIONAL CROPS:

Treated areas may be replanted with any crop specified on both clothianidin and beta-cyfluthrin labels, or any crop for which a tolerance exists for both active ingredients, as soon as practical following the last application. Areas planted with treated seed may be replanted immediately with cotton, corn, sorghum, rapeseed and canola. These areas may also be replanted after 30 days with cereal grains, soybeans, dried beans and dried peas. Do not plant any other crop in the treated area for at least one year after treated seeds are planted.

LABELING OF TREATED SEED

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Seed commercially treated with Poncho Beta must be labeled or tagged as follows:

- This seed has been treated with Poncho Beta, which contains clothianidin and beta-cyfluthrin.
- Do not use treated seed for food, feed or oil processing.
- Store away from feeds and foodstuffs.
- Wear long-sleeved shirt, long pants and waterproof gloves when handling treated seed.

- Dispose of all excess treated seed. Left over treated seed may be double own around the headland or buried away from water sources in accordance with local requirements. Do not contaminate water bodies when disposing of planting equipment washwaters.
- Dispose of seed packaging in accordance with local requirements.
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LIMITATIONS OF LIABILITY: TO THE EXTENT CONSISTENT WITH APPLICABLE LAW, THE EXCLUSIVE REMEDY OF THE USER OR BUYER FOR ANY AND ALL LOSSES, INJURIES OR DAMAGES RESULTING FROM THE USE OR HANDLING OF THIS PRODUCT, WHETHER IN CONTRACT, WARRANTY, TORT, NEGLIGENCE, STRICT LIABILITY OR OTHERWISE, SHALL NOT EXCEED THE PURCHASE PRICE PAID, OR AT BAYER CROPSOURCE'S ELECTION, THE REPLACEMENT OF PRODUCT.

NOTICE TO BUYER

Purchase of this material does not confer any rights under patents governing this product or the use thereof in countries outside of the United States.

NET CONTENTS:

Produced for



Bayer CropScience

Bayer CropScience LP
P.O. Box 12014, 2 T.W. Alexander Drive
Research Triangle Park, North Carolina 27709
1-866-99BAYER (1-866-992-2937)
<http://www.bayercropscienceus.com>

Poncho Beta (PENDING) Submitted 12/01/06, Resubmitted 03/06/08

FEE

DATE OUT: 28 Sept 2007

SUBJECT: PRODUCT CHEMISTRY REVIEW MP [] EP [x]
DP BARCODE No.: D335243
Reg. File Symbol No.: 264-RNLA
PRODUCT NAME: Poncho Beta
COMPANY: Bayer CropScience LP
Decision No.: 372785 PC CODE: 044309, 118831
FOOD USE: [x] Integrated Formulation []

FROM: Bruce F. Kitchens, Chemist
Technical Review Branch
Registration Division (7505P)

TO: RM #01, Venus Eagle/Kable Davis
Insecticide-Rodenticide Branch (7505P)
Registration Division (7505P)

Bruce F. Kitchens
28 Sept 2007

SBM 10/02/07

INTRODUCTION:

The registrant, Bayer CropScience LP, is submitting an application to register the proposed end-use product, Poncho Beta. The active ingredients in this product are Clothianidin and beta-Cyfluthrin at label nominal concentrations of 34.3 and 4.6% a.i., respectively. This product is intended for use as a sugar beet seed treatment. In support of this request, the registrant has submitted a basic and three alternate Confidential Statements of Formula (CSF) dated 01 Nov 2006, 02 Nov 2006, 03 Nov 2006, and 04 Nov 2006 respectively for the basic and three alternate formulas. This submission also includes a draft label and product chemistry data contained in MRID# 470078-01. The Technical Review Branch (TRB) has been asked to review this submission.

SUMMARY OF FINDINGS

TRB has reviewed this submission and reports the following findings:

1. This product is produced from registered sources of the active ingredient.
2. All inert ingredients are cleared for use in formulated pesticide products. In addition, all inert ingredients are exempt from the requirement of a food tolerance.
3. The nominal concentrations of the active ingredients listed on the proposed basic and alternate CSFs and the draft label are the same.
4. The draft label contains the appropriate storage and disposal statements.
5. The active ingredients' certified limits as proposed on the basic and alternate CSFs are acceptable.

CONCLUSIONS:

TRB has reviewed this submission and concludes the following:

1. The basic and alternate formula CSFs for the proposed end-use product, Poncho Beta dated 01 Nov 2006, 02 Nov 2006, 03 Nov 2006, and 04 Nov 2006 respectively, for the basic and three alternate formulas, are acceptable.
2. This submission (MRID# 470078-01) satisfies the data requirements as specified in 40 CFR 158.155, 158.160, 158.165, 158.167, 158.175, and 158.180 with respect to product identity and composition, description of materials used to produce the product, description of formulation process, discussion of formation of impurities, certified limits, and enforcement analytical method.
3. Except for storage stability/corrosion characteristics studies, the remaining product chemistry Group B data (MRID# 470078-01) adequately address the data requirements. The registrant states that storage stability and corrosion characteristics are in progress. Inform the registrant that these studies must be submitted to the Agency for evaluation upon completion.

PRODUCT CHEMISTRY DATA (SERIES 830 Subgroup A)

Subgroup A – Product Identity and Composition	<u>Data Required Fulfilled</u>	<u>MRID No.</u>
830.1550. Chemical Identity	Y	470078-01
830.1600. Beginning Materials	Y	470078-01
830.1650. Formulation Process	Y	470078-01
830.1670. Discussion of Impurities	Y	470078-01
830.1700. Preliminary Analysis	NA	
830.1750. Certified Limits	Y	470078-01
830.1800. Enforcement Analytical Method	Y	470078-01

Enforcement Analytical Method: (MRID No. 470078-01)

The active ingredient content in Poncho Beta is determined by different analytical methods. Clothianidin content was determined by reverse high performance liquid chromatography (HPLC) using ultraviolet detection (UV) at 270 nm and an external standard. This method was validated for linearity, precision, accuracy, interference from excipients, and specificity.

Beta-Cyfluthrin content was determined by gas chromatography (GC) using flame ionization detection (FID) and an internal standard. This method was validated for linearity, precision, accuracy, interference from excipients, and specificity.

#264-RNLA Poncho Beta
P.C. Codes 044309, 118831



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION,
PESTICIDES AND TOXIC SUBSTANCES

October 30, 2007

MEMORANDUM

Subject: EPA File Symbol: #264-RNLA Poncho Beta
DP Barcode: 335246
Decision No: 372786
PC Code: 044309, 118831
Action Code R17.2

From: Masih Hashim, Toxicologist
Technical Review Branch
Registration Division (7505C)

Mo
Byron T. B...
10-30-2007

To: Kable Davis, RM Team 01
Insecticide-Rodenticide Branch
Registration Division

Applicant: Bayer CropScience
Research Triangle Park, NC 27709

FORMULATION FROM LABEL:

<u>Active Ingredient(s):</u>	<u>% by wt.</u>
Clothianidin	34.3
Beta-Cyfluthrin	4.6
Inert Ingredients	<u>61.1</u>
Total:	100.0

ACTION REQUIRED: The Risk Manager requested a review of the acute toxicity data for the File Symbol #264-RNLA, an insecticide from Bayer CropScience.

BACKGROUND: A pack of six acute toxicity studies was submitted by Bayer CropScience to support the registration of Poncho Beta. The acute toxicity studies were conducted by Toxicology Laboratory of Bayer AG Laboratory, Wuppertal, Germany. An Agency Contractor, Oak Ridge National Laboratory (ORNL) conducted the primary review of the studies. TRB performed the secondary review and made changes as necessary.

RECOMMENDATIONS: Each of the six studies (MRID 47007802-07) is in compliance with Sub-Division F guidelines.

The toxicology profile for #264-1056 is as follows:

acute oral toxicity	III	acceptable	MRID 47007802
acute dermal toxicity	III	acceptable	MRID 47007803
acute inhalation study	IV	acceptable	MRID 47007804
primary eye irritation	IV	acceptable	MRID 47007805
primary dermal irritation	IV	acceptable	MRID 47007806
dermal sensitization	neg.	acceptable	MRID 47007807

LABELING:

#264-1056 Poncho Beta

Harmful if absorbed through skin. Harmful if swallowed. Avoid contact with skin or clothing. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Wear long-sleeved shirt and long pants, socks, shoes, and gloves. Remove and wash contaminated clothing before reuse. Wear appropriate protective clothing (optional).

Signal Word CAUTION

First Aid:

If on skin:

- Take off contaminated clothing.
- Rinse skin immediately with plenty of water for 15-20 minutes.
- Call a poison control center or doctor for treatment advice.

If swallowed:

- Call a poison control center or doctor immediately for treatment advice.
- Have person sip a glass of water if able to swallow.
- Do not induce vomiting unless told to by a poison control center or doctor.
- Do not give anything to an unconscious person.

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DATA EVALUATION RECORD

BETA-CYFLUTHRIN and CLOTHIANIDIN

STUDY TYPE: ACUTE ORAL TOXICITY - RAT [OPPTS 870.1100; OECD 423]
ACUTE DERMAL TOXICITY - RAT [OPPTS 870.1200; OECD 402]
ACUTE INHALATION TOXICITY - RAT [OPPTS 870.1300; OECD 403]
ACUTE EYE IRRITATION - RABBIT [OPPTS 870.2400; OECD 405]
ACUTE DERMAL IRRITATION - RABBIT [OPPTS 870.2500; OECD 404]
SKIN SENSITIZATION- GUINEA PIG [OPPTS 870.2600; OECD 406]

MRID 47007802, 47007803, 47007804, 47007805, 47007806, 47007807 and 47007808

Prepared for
Registration Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202

Prepared by
Toxicology and Hazard Assessment Group
Environmental Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 1-2

Primary Reviewer:
Dana F. Glass, D.V.M.

Secondary Reviewers:
Jennifer Rayner, Ph.D

Robert H. Ross, M.S., Group Leader

Quality Assurance:
Kim Slusher, M.S.

Signature:

Date:

Dana F. Glass

SEP 10 2007

Signature:

Date:

Jennifer Rayner

SEP 10 2007

Signature:

Date:

Robert H. Ross

SEP 10 2007

Signature:

Date:

Kim Slusher

SEP 10 2007

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

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Reviewer: ORNL
Risk Manager (EPA): 01

Date: September 7, 2007

STUDY TYPE: Acute Oral Toxicity – Rat; OPPTS 870.1100; OECD 423

TEST MATERIAL: FCR 4545 53.3 FS & TI 0435 400 (β-Cyfluthrin and Clothianidin) (FCR 4545- 57.14 g/L and TI 0435- 392.18 g/L; Batch No. 07847/0020 (0007); light beige suspension)

SYNONYMS: Not reported

CITATION: Krötlinger, F. 2002. Acute oral toxicity study in rats. Study No. T9071461 BAYER CropScience AG. Wuppertal, Germany. May 13, 2002. MRID 47007802.

SPONSOR: Not provided.

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 47007802), three HsdCpb:WU Wistar rats/sex/group (age 8-11 wks, wt. 170-274 g males, and 143-194 g females, source Harlan Winkleman, GmbH, Borcheln, Germany) were given a single oral dose of FCR 4545 53.3 FS & TI 0435 400 at a dose of 200, 500 or 2000 (females only) mg/kg bw by gavage and observed for 14 days. Animals were fasted prior to dosing.

All females died that were exposed to 2000 mg/kg by day 2. No animals died in the 200 or 500 mg/kg groups. Clinical signs were observed in the 2000 mg/kg females 40 minutes after dosing and included: decreased motility, uncoordinated gait, labored breathing, narrowed palpebral fissure, increased salivation and temporary rolling over. All treated animals in the 500 mg/kg group had clinical signs that included: decreased motility, uncoordinated gait, labored breathing, and increased salivation. Treatment did not affect the body weight of any of the animals. Animals dying during the study were observed to have dark red discoloration of the liver and slightly collapsed lungs. No findings were observed in the animals sacrificed at the end of the study.

LD₅₀ Males = >500 mg/kg
LD₅₀ Females = >500 mg/kg (according to OECD Guideline 423)
LD₅₀ Combined = >500 mg/kg

FCR 4545 53.3 FS & TI 0435 400 has an LD₅₀ >500 mg/kg and is in EPA Toxicity Category III.

This study is classified as acceptable. It does satisfy the guideline requirements for an acute oral study (OPPTS 870.1100; OECD 423) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance and No Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Submitter did not follow OECD 425 but instead followed OECD 423; therefore the up and down data were not included.

Animals were dosed as follows:

Animal Number	Sex	Dose Level (mg/kg)	Long-Term Outcome
1	M	200	S
2	M	200	S
3	M	200	S
4	M	500	S
5	M	500	S
6	M	500	S
7	F	200	S
8	F	200	S
9	F	200	S
10	F	500	S
11	F	500	S
12	F	500	S
13	F	2000	D
14	F	2000	D
15	F	2000	D

S = Survival, D = Death

- A. **Mortality**: All females dosed with 2000 mg/kg died by day 2. No other rats died.
- B. **Clinical observations**: Clinical signs were observed in the 2000 mg/kg females 40 minutes after dosing and included: decreased motility, uncoordinated gait, labored breathing, narrowed palpebral fissure, increased salivation and temporary rolling over. All treated animals in the 500 mg/kg group had clinical signs that included: decreased motility, uncoordinated gait, labored breathing, and increased salivation. Males in the 500 mg/kg group also had temporary rolling over, bradypnea and temporary broad legs and females in this group had piloerection. One 500 mg/kg male had spastic gain and one 500 mg/kg female had broad gait and temporary creeping gait. Treatment did not affect the body weight of any of the animals.
- C. **Gross necropsy**: All females that died in the 2000 mg/kg group had discolored livers and slightly collapsing lungs. All of the rats sacrificed at the end of the study had no abnormalities observed at necropsy.
- D. **Reviewer's conclusions**: This study was conducted according to OECD 423 and not OECD 425. The test formulation is in EPA Tox Category III based on its LD50 >500 mg/kg.

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Reviewer: ORNL
Risk Manager (EPA): 01

Date: September 7, 2007

STUDY TYPE: Acute Dermal Toxicity – Rat; OPPTS 870.1200; OECD 402

TEST MATERIAL: FCR 4545 53.3 FS & TI 0435 400 (β-Cyfluthrin and Clothianidin) (FCR 4545- 57.14 g/L and TI 0435- 392.18 g/L; Batch No. 07847/0020 (0007); light beige suspension)

SYNONYMS: Not reported

CITATION: Krötlinger, F. 2002. Acute dermal toxicity study in rats. Study No. T0071462, BAYER CropScience AG. Wuppertal, Germany. May 27, 2002. MRID 47007803.

SPONSOR: Not provided

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 47007803), five HsdCpb:WU Wistar rats/sex/group rats (age 9-12 wks, wt. 227-242 g males, and 211-224 g females, source Harlan Winkleman, GmbH, Borcheln, Germany) were dermally exposed on the shaved dorsal trunk to 4000 mg/kg FCR 4545 53.3 FS & TI 0435 400 under a occluded bandage for 24 hours. The animals were observed for 14 days.

All animals survived. All treated rats had local yellow discoloration from day 3 until day 14 in the treated area; however, no clinical signs were observed. Body weight was not affected with treatment, and there were no gross pathological changes at necropsy.

LD₅₀ Males > 4000 mg/kg bw
LD₅₀ Females > 4000 mg/kg bw
LD₅₀ Combined > 4000 mg/kg bw

FCR 4545 53.3 FS & TI 0435 400 has a dermal LD₅₀ > 4000 mg/kg and is in EPA Toxicity Category III.

This study is classified as acceptable. It does satisfy the guideline requirements for an acute dermal study (OPPTS 870.1200; OECD 402) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Dose (mg/kg bw)	Mortality/Number Tested		
	Males	Females	Combined
4000	0/5	0/5	0/10

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- A. **Mortality:** All animals survived the study.
- B. **Clinical observations:** The only clinical observation was a yellow discoloration in the treated area in all animals that was observed from day 3 to day 14.
- C. **Gross necropsy:** No findings were observed on necropsy.
- D. **Reviewer's conclusions:** This reviewer agrees with the study author. The formulation is in EPA Tox Category III for dermal toxicity based on the dermal LD50 > 4000 mg/kg.

Reviewer: ORNL
Risk Manager (EPA): 01

Date: September 7, 2007

STUDY TYPE: Acute Inhalation Toxicity -- Rat; OPPTS 870.1300; OECD 403

TEST MATERIAL: FCR 4545 53.3 FS & TI 0435 400 (β-Cyfluthrin and Clothianidin) (FCR 4545- 57.14 g/L and TI 0435- 392.18 g/L; Batch No. 07847/0020 (0007); light beige suspension)

SYNONYMS: Not reported

CITATION: Pauluhn, J. 2002. Study on acute inhalation toxicity in rats according to OECD No. 403. Study No. T5071467. BAYER CropScience AG. Wuppertal, Germany. July 1, 2002. MRID 47007804.

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID 47007804), five (SFP) HsdCpb:WU Wistar rats/sex/group (age 2 months old, wt. 165-183 g males, and 164-178 g females, source Harlan Winkleman, GmbH, Borcheln, Germany) were exposed by nose-only inhalation to FCR 4545 53.3 FS & TI 0435 400 for 4 hours at a concentration of 0 or 2671 mg/m³. The target concentration was 5000 mg/m³ but was not achieved. The animals were observed for 14 days. The average MMAD was 3.4 μm and the average GSD was 2.0.

No mortality occurred during the study. Body weight was not affected by treatment. All females and males exposed to 2671 mg/m³ exhibited the following clinical signs: piloerection, ungroomed hair coat, bradypnea, labored breathing, salivation, decreased motility, tremors, uncoordinated gait, and choreathetotic convulsions. After day 3, no other clinical signs were observed. A statistically significant ($p \leq 0.01$) decrease in body temperature was also observed in treated animals along with a transient decrease in body weight gain when compared to controls. No findings were observed on necropsy in any of the animals.

LC₅₀ Males > 2671 mg/m³ or 2.67 mg/L
LC₅₀ Females > 2671 mg/m³ or 2.67 mg/L
LC₅₀ Combined > 2671 mg/m³ or 2.67 mg/L

FCR 4545 53.3 FS & TI 0435 400 has an LC₅₀ >2.671 mg/kg and is in EPA Toxicity Category IV.

This study is classified as acceptable. It does satisfy the guideline requirements for an acute inhalation study (OPPTS 870.1300; OECD 403) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance and No Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Nominal Conc. (mg/L)	Gravimetric Conc. (mg/L)	MMAD μm	GSD	Mortality/Number Tested		
				Males	Females	Combined
16.32	1.44	3.4	2.0	0/5	0/5	0/10

Test Atmosphere / Chamber Description: Animals were exposed to aerosolized test material in Plexiglass exposure tubes applying a directed-flow nose-only principle. Tubes were designed to allow the rat's tail to be outside of the tube. A modified BG1 3-nozzle collision nebulizer (Type CN-25 MRE, BGI, Inc., Waltham, MA) was used which has a built in pre-separator/baffle system to allow the formation of fine particles. The nebulization used conditioned, pressurized air (15 L/min) and the test atmosphere was directly placed into the inhalation chamber. The inhalation chamber had the dimensions of 14 x 35 x 25 cm with an internal volume of about 3.8 L. During the exposure, the reservoir of the nebulizer was exchanged hourly to avoid changes in the concentration. Temperature was maintained using a digitally controlled thermostat.

Gravimetric Conc. (mg/L):	1.44
Chamber Volume (L):	3.8
Airflow (L/min):	15
Temperature	21.4- 22.3°C
Relative Humidity	$\geq 95\%$
Time to equilibrium:	Within 1 st minute

Test Atmosphere Concentration – Gravimetric samples were collected from the breathing zone of the animals using a glass fiber filter. The number of samples taken was sufficient to characterize the test atmosphere and adjusted to accommodate the sampling duration. Nominal concentration was calculated from the ratio of the quantity of test material nebulized and the total amount of air put through the inhalation chamber.

Particle Size Determination – Samples for analysis of particle size were taken in the breathing zone and analysis was done using a BERNER-TYPE AERAS low-pressure critical orifice cascade impactor. The individual impactor stages were covered by an aluminum foil and glass fiber filter which were subjected to gravimetric analysis. This analysis was made using a digital balance. The mass median aerodynamic diameter and particle size distributions were calculated.

A. **Mortality:** No mortalities occurred during the exposure.

B. **Clinical observations:** Body weight was not affected by treatment. Reflexes were checked on all animals on day 1 and no abnormalities were found in either males or females. All females and males exposed to 2671 mg/m³ exhibited the following clinical signs: piloerection, ungroomed hair coat, bradypnea, labored breathing, salivation, decreased motility, tremors, uncoordinated gait, and choreathetotic convulsions. After day 3, no other clinical signs were observed. A statistically significant ($p \leq 0.01$) decrease in body temperature was also observed in treated animals along with a transient decrease in body weight gain when compared to controls.

C. **Gross necropsy:** No abnormalities were observed in any rats at gross necropsy.

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D. Reviewer's conclusions: This reviewer agrees with the study author. The product is in EPA Tox Category IV based on its LC50 >2.671 mg/L.

Reviewer: ORNL
Risk Manager (EPA): 01

Date: September 7, 2007

STUDY TYPE: Primary Eye Irritation – Rabbit (Himalayan); OPPTS 870.2400; OECD 405

TEST MATERIAL: FCR 4545 53.3 FS & TI 0435 400 (β-Cyfluthrin and Clothianidin) (FCR 4545- 57.14 g/L and TI 0435- 392.18 g/L; Batch No. 07847/0020 (0007); light beige suspension) pH 5.5 (1% solution).

CITATION: Leuschner, P.J. 2002. Acute eye irritation study of FCR 4545 53.3 FS & TI 0435 400 by instillation into the conjunctival sac of rabbits. LPT Report No. 9301/544/95, Bayer Study No. T 5070792, Report No. R-8159A. LPT Laboratory of Pharmacology and Toxicology KG, Hamburg, Germany. April 25, 2002. MRID 47007805

SPONSOR: BAYER CropScience AG, Wuppertal, Germany

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 47007805), 0.1 mL of undiluted FCR 4545 53.3 FS & TI 0435 400 was instilled into the conjunctival sac of the right eye of three male Himalayan rabbits (age 4.5-5.0 months, wt. 1.9-2.2 kg, source: LPT Laboratory of Pharmacology and Toxicology KG, Wankendorf). The untreated left eye served as a control. After the administration, rabbits were kept in restrainers that prevented a complete body turn but allowed free movement of the head. Eyes were examined ophthalmoscopically prior to administration and at 1, 24, 48 and 72 hours afterwards or until all findings subsided. Eyes were also stained with fluorescein 24 hours after administration.

All animals had conjunctival redness (grade 1 or 2) and conjunctival chemosis (grade 1) one hour after instillation. One of the rabbits continued to have grade 1 conjunctival redness until 24 hours. No effects were observed on the iris or cornea.

In this study, the formulation is slightly irritating. FCR 4545 53.3 FS & TI 0435 400 is classified as EPA Toxicity Category IV for primary eye irritation.

This study is classified as acceptable. It does satisfy the guideline requirements for a primary eye irritation study (OPPTS 870.2400; OECD 405) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance and No Data Confidentiality statements were provided.

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RESULTS and DISCUSSION:

Observations	No. positive/No. tested				
	hours				
	Prior to administration	1	24	48	72
Corneal Opacity	0/3	0/3	0/3	0/3	0/3
Iritis	0/3	0/3	0/3	0/3	0/3
Conjunctivae					
Redness*	0/3	2/3	0/3	0/3	0/3
Chemosis*	0/3	0/3	0/3	0/3	0/3
Discharge**	NR	NR	NR	NR	NR

NR= not reported

*Score of 2 or more required to be considered "positive"

** Discharge does not indicate a positive effect according to the grading scale

- A. **Observations:** All animals had conjunctival redness (grade 1 or 2) and conjunctival chemosis (grade 1) one hour after instillation. One of the rabbits continued to have grade 1 conjunctival redness until 24 hours. No effects were observed on the iris or cornea. Fluorescein staining showed no pathological findings.
- B. **Results:** FCR 4545 53.3 FS & TI 0435 400 is considered slightly irritating.
- C. **Reviewer's conclusions:** This reviewer agrees with the study author that the test material is slightly irritating to the eye, and is in EPA Tox Category IV for eye irritation.

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Reviewer: ORNL
Risk Manager (EPA): 01

Date: September 7, 2007

STUDY TYPE: Primary Dermal Irritation – Rabbit (Himalayan); OPPTS 870.2500; OECD 404

TEST MATERIAL: FCR 4545 53.3 FS & TI 0435 400 (β -Cyfluthrin and Clothianidin) (FCR 4545- 57.14 g/L and TI 0435- 392.18 g/L; Batch No. 07847/0020 (0007); light beige suspension) pH 5.5 (1% solution).

CITATION: Leuschner, P.J. 2002. Acute skin irritation test (patch test) of FCR 4545 53.3 FS & TI 0435 400 in rabbits. LPT Report No. 9300/544/95, Bayer Study No. T 5070792, Report No. R-8160. LPT Laboratory of Pharmacology and Toxicology KG, Hamburg, Germany. April 25, 2002. MRID 47007806

SPONSOR: BAYER CropScience AG, Wuppertal, Germany

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 47007806), three male Himalayan rabbits (age 6.5-8.5 months, wt. 2.0-2.1 kg, source: LPT Laboratory of Pharmacology and Toxicology KG, Wankendorf) were dermally exposed to 0.5 mL of FCR 4545 53.3 FS & TI 0435 400 for 4 hours on an area of shaved intact dorsal skin. The area of application was covered with a semi-occlusive dressing. Observations for dermal irritation and defects were made at 1, 24, 48 and 72 hours and up until 14 days if effects were observed.

No abnormalities or irritation were observed in any of the rabbits when observed up to 72 hours.

In this study, the formulation is not irritating. FCR 4545 53.3 FS & TI 0435 400 is classified as EPA Toxicity Category IV for primary dermal irritation.

This study is classified as acceptable. It does satisfy the guideline requirements for a primary dermal irritation study (OPPTS 870.2500; OECD 404) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance and No Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Animal Number	Sex	Hours			
		1*	24	28	72
1	M	0	0	0	0
2	M	0	0	0	0
3	M	0	0	0	0
Severity of Irritation – Mean Score		0	0	0	0

*Erythema

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- A. **Observations:** No edema or erythema was observed in any of the 3 treated males. Body weight was also not affected with treatment.
- B. **Results:** FCR 4545 53.3 FS & TI 0435 400 is not irritating. Primary Irritation Index (PII) is 0.0.
- C. **Reviewer's conclusions:** This reviewer agrees with the study author that the test material is not irritating to skin. The product is in EPA Tox Category IV.

Reviewer: ORNL
Risk Manager (EPA): 01

Date: September 7, 2007

STUDY TYPE: Dermal Sensitization – guinea pig; OPPTS 870.2600; OECD 406

TEST MATERIAL: FCR 4545 53.3 FS & TI 0435 400 (β-Cyfluthrin and Clothianidin) (FCR 4545- 57.14 g/L and TI 0435- 392.18 g/L; Batch No. 07847/0020 (0007); light beige suspension)

SYNONYMS: None provided

CITATION: Vohr, H.W. 2002. Study for the skin sensitization effect in guinea pigs (guinea pig maximization test according to Magnusson and Kligman). Study No. T5071827. BAYER CropScience AG. Wuppertal, Germany. July 1, 2002. MRID 47007807

SPONSOR: Not provided

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 47007807) using the guinea pig maximization test (GPMT), twenty female Hsd Poc:DH guinea pigs (age 5-6 weeks, wt. 266-345g source: Harlan Winkelmann GmbH Laboratory Animal Breeders, Borcheln) were used as the test animals and ten females were used as the controls. An additional two animals were used for dose-finding. Doses for the induction and challenge treatments were as follows: intradermal induction- 5% (20 mg test material/animal); topical induction- 100% (500 mg test material/animal) and challenge- 100% (500 mg test material/animal).

Clinical signs were not observed and body weight was not affected with treatment. After the intradermal induction, control animals had red wheals and the treated animals had red wheals, a red injection site and wheals with encrustation. After 7 days, the controls had wheals at the injection site and the treated animals had wheals and encrustations. After the challenge, no effects were observed in any of the guinea pigs.

Based on the results of this study, FCR 4545 53.3 FS & TI 0435 400 is not a dermal sensitizer.

This study is classified as acceptable. It does satisfy the guideline requirements for a dermal sensitization study (OPPTS 870.2600; OECD 406) in the guinea pig.

COMPLIANCE: Signed and dated GLP, Quality Assurance and No Data Confidentiality statements were provided.

PROCEDURE:

- A. **Induction:** Intradermal Induction: All animals had the dorsal region and flanks shaved on the day prior to testing. The test material was formulated in sterile physiological saline solution. Starting behind the nape of the neck, three injections of 0.1 mL each were made in a row on the right and left side of the spinal column. The 1st and 2nd injections were made as close as possible and the 3rd about 2 cm from the 2nd. The test group animals had Freund's adjuvant in the 1st injection site and 5% test material in the 2nd and 3rd site. Both were mixed with saline solution. Injection sites were assessed visually on days 2 and 7.

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Topical induction: The area was again shaved one day prior to the topical induction. One week after the intradermal induction, hypoallergic patches (2 x 4 cm) treated with 0.5 mL 100% FCR 4545 53.3 FS & TI 0435 400 were placed between and on the injection sites, covered with aluminum foil and held in place with ORABAND self-adhesive tape. After 48 hours, the patch was removed and the area washed with sterile saline.

- B. **Challenge:** The challenge was performed three weeks after the intradermal induction with the animals again shaved prior to starting the challenge. A hypoallergic patch treated with 100% test material was placed on the caudal right flank of the animals in both the test and control groups. ORABAND self-adhesive tape was used to hold in place for 24 hours. A dry patch was also placed on the cranial right flank to be used as a control.
- C. **Naïve controls:** Intradermal Induction: The control animals had the same procedure as the treated animals but the formulation for injection sites 2 and 3 did not contain any test material. In site 2, there was undiluted vehicle and in site 3, there was a 1:1 mixture FCA/Vehicle. The injection sites were visually assessed on days 2 and 7.

Topical induction: The area was again shaved one day prior to the topical induction. One week after the intradermal induction, hypoallergic patches (2 x 4 cm) left dry were placed between and on the injection sites, covered with aluminum foil and held in place with ORABAND self-adhesive tape. After 48 hours, the patch was removed and the area washed with sterile saline.

RESULTS and DISCUSSION:

- A. **Reactions and durations:** Clinical signs were not observed and body weight was not affected with treatment. After the intradermal induction, control animals had red wheals and the treated animals had red wheals, a red injection site and wheals with encrustation. After 7 days, the controls had wheals at the injection site and the treated animals had wheals and encrustations. After the challenge, no effects were observed in any of the guinea pigs.
- B. **Positive control:** Positive control data were not provided in the study report but the report stated that the sensitivity in this strain of guinea pigs had been conducted by the lab (Vohr, 2001) and appropriate reliability of the technique was checked at regular intervals. Records regarding this are maintained at Bayer AG archives.
- C. **Reviewer's conclusion:** The reviewer agrees with the conclusion that FCR 4545 53.3 FS & TI 0435 400 is not a dermal sensitizer.

1. **DP BARCODE:** DP335246
2. **PC CODES:** 118831, 044309
3. **CURRENT DATE:** September 7, 2007
4. **TEST MATERIAL:** FCR 4545 53.3 FS & TI 0435 400 (β-Cyfluthrin and Clothianidin)
(FCR 4545- 57.14 g/L and TI 0435- 392.18 g/L; Batch No. 07847/0020 (0007); light beige suspension)

Study/Species/Lab Study # / Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat BAYER CropScience AG T9071461/May 13, 2002	47007802	LD ₅₀ females > 500 <1000 mg/kg males >500 mg/kg	III	A
Acute dermal toxicity/rat BAYER CropScience AG T0071462/May 27, 2002	47007803	LD ₅₀ Males > 4000 mg/kg bw LD ₅₀ Females > 4000 mg/kg bw LD ₅₀ Combined > 4000 mg/kg bw	III	A
Acute inhalation toxicity/rat BAYER CropScience AG T5071467/July 1, 2002	47007804	LC ₅₀ Combined > 2671 mg/m ³ or 2.67 mg/L	IV	A
Primary eye irritation/rabbit LPT Laboratory of Pharmacology and Toxicology KG T5070792/April 25, 2002	47007805	Slightly irritating	IV	A
Primary dermal irritation/rabbit LPT Laboratory of Pharmacology and Toxicology KG T5070792/April 25, 2002	47007806	Not irritating	IV	A
Skin sensitization study/guinea pig BAYER CropScience AG T5071827/ July 1, 2002	47007807	Not a dermal sensitizer	-	A

Core Grade Key: A = Acceptable, S = Supplementary, U = Unacceptable, W = Waived

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

October 16, 2007

MEMORANDUM

SUBJECT: Clothianidin: Human Health Risk Assessment for Proposed Use on Sugar Beet.
PC Code: 044309; Petition Number: 6F7159; DP Number: D344619.

Regulatory Actions: Section 3
Risk Assessment Type: Single Chemical/Aggregate

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1.0 Executive Summary

Background

Clothianidin [(E)-1-(2-chloro-1,3-thiazol-5-ylmethyl)-3-methyl-2-nitroguanidine], a major metabolite of the active ingredient thiamethoxam, is a systemic insecticide that belongs to the nitroguanidine sub-class of neonicotinoid compounds, which have agonistic activity on nicotinic acetylcholine receptors (nAChR). It enters through the roots and cotyledons of newly germinating seedlings and protects below- and above-ground plant parts from insect damage. Clothianidin is currently registered for use on corn, canola, pome fruit, tobacco, turf, ornamental plants, grapes, sorghum, potatoes, and cotton. Permanent tolerances are established for residues of clothianidin in/on plant and animal commodities (milk only) at 0.01-1.0 ppm. A time-limited tolerance at 0.02 ppm has been established for sugar beet roots and tops in conjunction with Section 18 uses in Oregon, Wyoming, Colorado, and North Dakota. Tolerances are also established for the indirect residues of clothianidin at 0.02 ppm in nongrass animal feeds; forage, fodder, and straw of cereal grains; forage, fodder, and hay of grasses; and soybean forage and hay.

Bayer CropScience has requested the establishment of permanent tolerances in sugar beet roots, tops, and molasses. The petitioner has proposed to use Poncho Beta, a multiple-active-ingredient (MAI) formulation containing 3.33 pounds per gallon (lb/gal) of clothianidin and 0.44 lb/gal of beta-cyfluthrin, on sugar beet seeds. This product is formulated as a suspo-emulsion (SE), which is a combination formulation consisting of a suspension concentrate coupled with an oil-based emulsion. The proposed use is restricted to commercial seed treatments; applications using equipment for treating seeds at planting are prohibited. For clothianidin, the proposed use rate is 0.132 lb active ingredient (ai) per 100,000 seeds, which is equivalent to 0.068-0.095 lb ai per acre (lb ai/A), based on typical planting rates of 53,000-72,000 seeds per acre.

Hazard Characterization

Clothianidin does not appear to exhibit toxicity towards a consistent specific target organ. Decreases in body weight and body weight gain were observed in rats, dogs, and mice. In single-dose studies, mice (acute toxicity category II) appear more sensitive than rats (category IV). Clinical signs of neurotoxicity were exhibited in both mice (decreased motor activity, tremors, and deep respirations at 50 mg/kg) and rats (transient signs of decreased arousal, motor activity, and locomotor activity at 100 mg/kg) in acute neurotoxicity studies following exposure by gavage; however, no indications of neurotoxicity were observed following dietary exposure in the subchronic neurotoxicity study in rats. In a developmental neurotoxicity study in rats, decreased body weights, body weight gains, motor activity, and acoustic startle response amplitude (females) were seen in offspring at doses lower than those resulting in maternal toxicity. Although the No Observed Adverse Effect Levels (NOAELs) were similar for the subchronic and chronic feeding studies in the rat, a greater spectrum of effects was observed in the chronic study (decreased body weight, body weight gain, and food consumption plus additional observations in the liver, ovary, and kidney) versus the subchronic study (effects only on body weight and food consumption). In the rat, administration via the oral route appears to be more toxic than via the dermal route. In longer term studies, dogs exhibited clinical signs of anemia. The only observed effects in mice following chronic dietary administration were

increases in vocalization and decreases in body weight and body weight gain. The Hazard Identification Assessment Review Committee (HIARC) classified clothianidin as not likely to be carcinogenic to humans.

There was no evidence of increased quantitative or qualitative susceptibility of rat or rabbit offspring in developmental studies; however, increased quantitative susceptibility of rat pups was seen in both the reproduction and developmental neurotoxicity studies. The degree of concern for both of these studies is low because the observed effects are well characterized, and there are clear NOAELs and Lowest Observed Adverse Effect Level (LOAELs). The NOAEL for the effects of concern identified in the reproduction study (decreased mean body weight gain and absolute thymus weights in pups, delayed sexual maturation, and an increase in still births) is the basis for the endpoint selected for the chronic dietary and short-, intermediate- and long-term non-dietary risk assessments.

In adult rats, a guideline immunotoxicity study shows no clothianidin-mediated immunotoxicity at doses lower than those resulting in generalized signs of toxicity (e.g., decreases in body weight); however, it cannot be concluded that a similar lack of effects will occur in offspring. Based on evidence of decreased absolute and adjusted organ weights of the thymus and spleen in multiple studies in the clothianidin data base and on evidence of increased quantitative susceptibility of juvenile rats, compared to adults, in the two-generation reproduction study to these effects, the Health Effects Division (HED) has recommended that a developmental immunotoxicity (DIT) study be conducted. Because results from the DIT could result in a more protective (i.e., lower) regulatory endpoint, a 10X database uncertainty factor (UF_{DB}) is applied to both single- and repeated-dose exposure scenarios (i.e., acute and chronic RfDs, short- and intermediate-term incidental oral exposures, and short-, intermediate-, and long-term dermal and inhalation exposures resulting from residential uses of clothianidin) to account for the lack of this study.

Residue Chemistry

The nature of the residue has been adequately delineated in plants, based on acceptable corn, sugar beet, apple, and tomato metabolism studies. HED has determined that the parent compound is the only residue of concern (ROC) in primary crops for both tolerance expression and risk assessment purposes. The nature of the residue in livestock is also understood, based on acceptable goat and hen metabolism studies. For ruminants, HED concluded that the ROCs for risk assessment include parent and the metabolites TZU, TZG, TZNG, and ATMG-Pyruvate; for poultry, HED concluded that the ROCs for risk assessment include parent and the metabolites TZU, TZG, TZNG, and ATG-Acetate. However, only parent needs to be included in the tolerance expression.

In general, adequate analytical methods, enforcement methods, storage stability data on parent clothianidin, field trial data, processing studies, livestock feeding studies, and rotational crop data are available to support the proposed sugar beet seed treatment use. Preliminary storage stability data on TMG support the current sugar beet field trials and processing studies; however, the final storage stability study on TMG has not been submitted to the Agency.

Dietary Exposure Assessment

Acute and chronic dietary exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.03). Because clothianidin is a major metabolite of thiamethoxam, residues of clothianidin resulting from uses of thiamethoxam were accounted for in these assessments. The acute assessment is based on maximum residues of clothianidin observed in clothianidin and thiamethoxam field trials and assumes 100% crop treated (%CT). The chronic assessment is based on average residues from clothianidin and thiamethoxam field trials and also assumes 100% crop treated. For crops that are registered for both thiamethoxam and clothianidin, residue estimates from each source were added together in order to estimate dietary exposure. This method of accounting for thiamethoxam's involvement in clothianidin exposure, when coupled with the assumption of 100% crop treated, likely overestimates that particular contribution to total exposure, as it results in a potential "double counting" of clothianidin coming from thiamethoxam for crops that have registered uses of both compounds. The empirical processing factor for apple juice was used for apple and pear juice, and empirical factors were used for grape juice, raisins, and sugar beet molasses; otherwise, DEEM default processing factors were used. The analyses include direct incorporation of estimated clothianidin residues in drinking water. For water, the highest acute estimate from conservative models was used for both the acute and the chronic dietary exposure analyses.

Based on these highly conservative assumptions, all acute and chronic dietary risk estimates are below HED's level of concern (LOC).

Residential Risk

Residential exposures to clothianidin are expected solely from currently registered uses, with no additional residential exposure expected from the proposed new use on sugar beet seeds. Subsequent to the risk assessment on the residential exposure to clothianidin, thiamethoxam has been registered for use on turf. Because the actions of these compounds are similar and because the thiamethoxam label recommends against the application of another Group 4A insecticide, it is highly unlikely that turf would be treated with thiamethoxam and clothianidin simultaneously. Since the duration of residential exposure to either compound is short-term, simultaneous exposure to clothianidin from both sources is highly unlikely. Residential exposure to clothianidin applied directly on turf is expected to be higher than exposure to clothianidin residues when thiamethoxam is applied on turf, so previously calculated risks for the use of clothianidin, *per se*, on turf are considered protective of residential exposure to clothianidin as either an active ingredient or a metabolite of thiamethoxam.

A margin of exposure (MOE) of 1000 or more is sufficient to protect adults and children from residential exposures to clothianidin. The residential risks associated with post-application exposure to clothianidin residues do not exceed HED's level of concern for the general U.S. population or any population subgroup.

Aggregate Risk

The acute aggregate assessment for clothianidin exposure includes only food and water exposures. Short- and intermediate-term aggregate assessments were conducted based on food, water, and residential exposures. The long-term aggregate risk assessment includes only

food and water since no long-term exposure scenarios are expected from residential uses of clothianidin. Because clothianidin has been classified as a "not likely human carcinogen," cancer risk is not a concern. Estimates of acute, short-term, intermediate-term, and long-term aggregate risks associated with the registered and proposed uses of clothianidin do not exceed HED's level of concern for the general U.S. population or any population subgroup.

Occupational Risk

Occupational exposure assessments were conducted for both handler and post-application exposures for the sugar beet seed treatment use. The treatment of sugar beet seeds may last more than a month due to the longer planting season; therefore, both short- and intermediate-term occupational exposures were assessed. A margin of exposure (MOE) of 100 or more is sufficient to protect workers from all of the handler and post-application occupational exposures to clothianidin. None of the risk estimates for any of the occupational scenarios examined in this assessment exceed HED's level of concern.

Environmental Justice Considerations

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," <http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf>.

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Surveys of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Whenever appropriate, nondietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies, which comprise the Pesticide Handlers Exposure Database (PHED), have been determined to require a review of their ethical conduct, and have received that review. The studies in PHED were considered appropriate (or ethically conducted) for use in risk assessments.

Recommendations

Based on the results of our assessment, HED recommends the establishment of the following permanent tolerances for residues of clothianidin, pending resolution of the deficiencies noted in

Section 10 of this document:

Beet, sugar, roots	0.02 ppm
Beet, sugar, tops	None
Beet, sugar, molasses	0.05 ppm
Beet, sugar, dried pulp	0.03 ppm

Additional Data Needs

See Section 10.

2.0 Ingredient Profile

Clothianidin is a systemic insecticide that belongs to the nitroguanidine sub-class of neonicotinoid compounds, which has agonistic activity on nicotinic acetylcholine receptors (nAChR). It is a metabolite of another neonicotinoid, thiamethoxam. Clothianidin enters through the roots and cotyledons of newly germinating seedlings and protects below- and above-ground plant parts from insect damage.

The chemical structure and nomenclature of clothianidin are presented in Table 2.1, and the physicochemical properties of the technical grade of clothianidin are presented in Table 2.2.

The end-use product for the proposed new use on sugar beet seeds is Poncho Beta, an MAI formulation containing 3.33 pounds per gallon (lb/gal) of clothianidin and 0.44 lb/gal of beta-cyfluthrin. This product is formulated as a suspo-emulsion (SE), which is a combination formulation consisting of a suspension concentrate coupled with an oil-based emulsion. The proposed use is restricted to commercial seed treatments; applications are prohibited that use equipment for treating seeds at planting. For clothianidin, the proposed use rate is 0.132 lb active ingredient (ai) per 100,000 seeds, which is equivalent to 0.068-0.095 lb ai per acre (lb ai/A), based on typical planting rates of 53,000-72,000 seeds per acre. The proposed directions for this new use of clothianidin are summarized in Table 2.3.

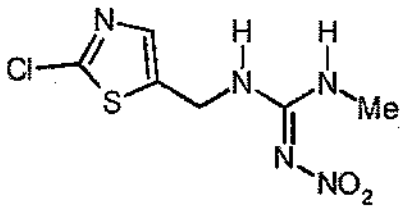
Table 2.1. Clothianidin Nomenclature.	
Chemical Structure	
Empirical Formula	C ₆ H ₈ ClN ₅ O ₂ S
Common name	Clothianidin
Company experimental name	TM-444, TI-435, V-10066
IUPAC name	(E)-1-(2-chloro-1,3-thiazol-5-ylmethyl)-3-methyl-2-nitroguanidine
CAS name	[C(E)]-N-[(2-chloro-5-thiazolyl) methyl]-N'-methyl-N''-nitroguanidine
CAS Registry Number	210880-92-5 (formerly 205510-53-8)
End-use product (EP)	Poncho Beta (3.33 lb ai/gal SE; EPA File Symbol 264-RNLA)
Chemical Class	Neonicotinoid (chloronicotinyl)
Known Impurities of Concern	None

Table 2.2. Physicochemical Properties of Clothianidin.		
Parameter	Value	Reference
Molecular weight	249.7	MRID 45422301
Melting point/range (°C)	176.8	
pH at 23°C	6.24 (1% solution/suspension)	
Density (g/cm ³) at 20°C	1.61 (PAD), 1.59 (TGAI)	
Water solubility (g/L) at 20°C	0.327	

Table 2.2. Physicochemical Properties of Clothianidin.		
Parameter	Value	Reference
Solvent solubility (g/L) at 25°C	Acetone	15.2
	Dichloromethane	1.32
	Ethyl acetate	2.03
	Heptane	<0.00104
	Methanol	6.26
	Octanol	0.938
	Xylene	0.0128
Vapor pressure (Pa) at 25°C	1.3 x 10 ⁻¹⁰	
Dissociation constant (pK _a) at 20°C	11.09	
Octanol/water partition coefficient (log K _{ow}) at 25°C	0.7	
UV/visible absorption spectrum, maximum (nm)	265.5 (acidic, neutral solutions)	
	246.0 (basic solution)	

Table 2.3. Summary of Proposed Directions for New Use of Clothianidin.						
Application Timing, Type, and Equipment ¹	Formulation [EPA File Symbol]	Application Rate (lb ai/100,000 seeds)	Maximum # of Uses per Season	Maximum Seasonal Use Rate (lb ai/A) ²	PHI (days)	Use Directions and Limitations
Sugar beet						
Seed treatment; prior to planting; commercial liquid or slurry treaters.	3.33 lb ai/gal SE ³ [264-RNLA]	0.132	1	0.069-0.095	N/A	All seeds treated must be conspicuously colored at the time of treatment. Do not use treated seed for food, feed, or oil processing.

¹ To be used only in liquid or slurry seed-treating equipment by commercial seed treaters. Do not use in farm equipment for seed treatment at the time of planting.

² Maximum field use rate, based on seeding rates of roughly 53,000-72,000 seeds per acre.

³ This formulation is an SE, which is a heterogeneous preparation consisting of a stable dispersion of the ai in the form of solid particles and fine globules in a continuous water phase. It is an MAI which also contains 0.44 lb/gal of beta-cyfluthrin.

3.0 Hazard Characterization/Assessment

3.1 Hazard and Dose-Response Characterization

The toxicology database for clothianidin is complete, with the exception of a developmental immunotoxicity study. The scientific quality is relatively high, and the toxicity profile of clothianidin can be characterized for most potential developmental, reproductive, neurotoxic, carcinogenic, and mutagenic effects. Clothianidin induces some effects that are similar to other neonicotinoid insecticides, particularly effects on the liver, hematopoietic system, and kidneys.

With the exception of the TMG metabolite, most of the metabolites and intermediates appear to be of similar toxicity to the parent technical material in acute oral studies. The TMG metabolite appears to be more toxic. In addition, the clothianidin-triazan intermediate tested as a dermal sensitizer under the conditions of the study, whereas the parent was not a dermal sensitizer.

Acute neurotoxicity studies were conducted in both rats and mice following exposure to

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clothianidin by gavage. Comparing these two studies, mice appear to be more sensitive than rats to the acute neurotoxic effects of clothianidin. In the acute neurotoxicity rat study, FOB effects, including decreased arousal and decreased motor and locomotor activity, were seen at the LOAEL on Day 0 in males. Effects at dose levels above the LOAEL in the rat study included tremors, slightly uncoordinated gait, effects on pupil response and righting reflex, decreases in body temperature, and ataxia. In the acute neurotoxicity study in mice, effects were also observed on Day 0 in males (no female mice were tested), but they occurred at lower dose levels than those that produced neurotoxic effects in rats. Effects seen at the LOAEL in this mouse study included transient signs of decreased spontaneous motor activity, tremors, and deep respirations. At higher dose levels, decreases in reactivity, grooming, and muscle tone; prone position; staggering gait; mydriasis; and hypothermia were observed in mice.

In rats only, a subchronic neurotoxicity study was conducted following dietary exposure to clothianidin. In contrast to the acute neurotoxicity study described previously, in which neurotoxic effects were observed after gavage exposure, no indications of neurotoxicity were noted in the subchronic study following dietary exposure. Slightly decreased food consumption, body weights, and body weight gains were the only observed effects in the subchronic neurotoxicity study.

In subchronic oral studies in rats and dogs, decreases in body weight and body weight gain were observed in both species. In addition, dogs also displayed decreased white blood cells, albumin, and total protein, as well as some anemia, and they appear to be more sensitive than rats to the effects of clothianidin following subchronic oral exposure. Following subchronic exposures, male dogs are more sensitive than females. No effects were observed up to the limit dose in the 28-day dermal study in rats.

Chronic feeding studies were conducted in the dog, rat, and mouse. Anemia was observed in the dog. In the rat, decreased body weight and food consumption, ovary interstitial gland hyperplasia, increased lymphohistiocytic infiltrate, and altered hepatocellular eosinophilic foci of the liver were observed in females; decreased body weight and food consumption, slightly increased incidences of pelvic mineralization, and transitional cell hyperplasia in the kidney, mottled livers, and altered hepatocellular eosinophilic foci in the liver were observed in male rats. In the mouse, decreases in body weight and body weight gain in females and increases in vocalization in both sexes were the only observed effects.

A comparison of the subchronic and chronic feeding studies in the rats shows that a wider spectrum of effects was observed in the chronic study, even though the NOAELs and LOAELs in these two studies were similar. Thus, it appears that there may be more toxicity in rats when exposure is over a longer period of time. In contrast, administration of clothianidin to the dog for a longer period of time does not appear to result in any additional effects or effects at lower dose levels.

In the developmental neurotoxicity study, toxicity in the offspring was observed at a lower dose level than the dose that caused toxicity in the maternal animals. Maternal effects included decreased body weights, body weight gains, and food consumption. Effects seen in the offspring

included decreased body weights, body weight gains, motor activity, and acoustic startle response in the females.

No quantitative or qualitative susceptibility was observed in either of the developmental rat or rabbit studies. In the rat, no developmental toxicity was observed at the highest dose tested, although this dose level induced decreases in body weight gain and food consumption in the dams. In the rabbit, premature deliveries, decreased gravid uterine weights, an increase in litter incidence of a missing lobe of the lung, and a decrease in the litter average for ossified sternal centra per fetus were noted at a dose level in which maternal death, a decrease in food consumption, and clinical signs (scant feces and orange urine) were observed. The developmental effects in this study are not considered to be quantitatively more severe than the maternal effects because they occurred at the same dose, and they are not considered to be qualitatively more severe because death occurred in the dams.

Quantitative susceptibility was observed in the two-generation reproduction study since the offspring NOAEL is lower than the parental NOAEL. The LOAEL for offspring toxicity is based on decreased body weight gains, delayed sexual maturation (males), decreased absolute thymus weights in F1 pups of both sexes, and an increase in stillbirths in both generations. The parental systemic LOAEL is based on decreased absolute body weights and body weight gains with decreased absolute and relative thymus weights in both sexes.

In the rat chronic feeding/carcinogenicity study, an apparent increase in thyroid c-cell tumors was observed in females. In addition, an increased incidence of hepatocellular carcinomas in males was examined more closely. A statistical analysis revealed that the increase in thyroid c-cell tumors did not appear to be significant, especially when carcinomas and adenomas are combined. The increased incidence of hepatocellular carcinomas at the low and high doses were just outside historical control incidences for the same testing laboratory (only 2 studies) but were within the historical control range for the animal supplier. In addition, there was no dose-response. Finally, there was no continuum (*i.e.*, no preneoplastic lesions and no adenomas). There was no evidence of an increase in tumors in mice. Therefore, clothianidin is classified as not likely to be carcinogenic to humans. Clothianidin is a major animal and plant metabolite of thiamethoxam. Thiamethoxam is not carcinogenic to male and female rats; however, dietary administration of thiamethoxam is associated with increased incidence of liver tumors in both sexes of mice. The fact that thiamethoxam induces liver tumors in mice and no tumors in rats supports the argument that clothianidin is not likely to be carcinogenic to humans because the apparent increases in tumors with clothianidin were in a different species (rats) and because the tumor of higher potential concern (thyroid) was not in the same target organ.

In the mutagenicity studies, none of the intermediates or metabolites appeared to have genotoxic potential under the conditions of the studies, but the studies for the technical material gave mixed results. Some of the batches of test material tested positively, and some tested negatively. The HIARC has requested that the composition of the test materials used in the mutagenicity studies be investigated to determine whether or not the differences in composition may have affected the results from the studies. Additional data on the composition of the materials has been submitted and is currently under review.

In some of the toxicological studies, there was evidence of possible effects on the immune system. Decreased absolute and adjusted thymus and spleen weights were observed in multiple studies. In addition, juvenile rats in the two-generation reproduction study appeared to be more susceptible to these effects. The thymus is involved in the production of T cells, whose function is to recognize and respond to foreign antigens. The spleen serves an important function in clearing the blood of infectious organisms. Even though a guideline immunotoxicity study showed no clothianidin-mediated immunotoxicity in adult rats, in the form of a T-cell dependent anti-SRBC-forming cell response, at doses lower than those resulting in generalized signs of toxicity (e.g., decreases in body weight), it cannot be concluded that a similar lack of effects will occur in offspring. Therefore, the Health Effects Division (HED) recommends a developmental immunotoxicity (DIT) study.

In rats, clothianidin was readily absorbed and excreted within 96 hours following a single low dose or repeated low doses, but at a high dose, absorption became biphasic and was saturated. The studies suggest that a multiple exposure regimen did not affect the absorption/excretion processes. There was rapid absorption and distribution of administered radioactivity to all organs and tissues followed by rapid excretion with reduction to background levels in most tissues and organs within 24 hours. There was a somewhat greater rate of absorption and elimination in females. Excretory patterns did not exhibit gender-related variability but reflected the delayed absorption in the high-dose group. The metabolites identified (primarily oxidative demethylation products and cleavage products of the nitrogen-carbon bond between the nitroimino and thiazolyl moieties) were consistent with Phase I processes.

In mice, clothianidin is readily absorbed and excreted within 168 hours following a single low dose. Urine was the major route of excretion. Neither clothianidin nor its metabolites appeared to exhibit potential for bioaccumulation. Excretory patterns did not exhibit gender-related variability. The major metabolites in both urine and feces were the parent compound (clothianidin) and TZNG [N-(2-chlorothiazol-5-ylmethyl)-N'-nitroguanidine], which resulted from N-demethylation of clothianidin.

A dermal absorption study with monkeys is available. In this study, dermal absorption was calculated at 0.24% (\pm 0.11%). This value was determined by adding the radioactivity recovered from urinary excretion, fecal excretion, and from Cage/Pan/Chair Wash, Debris. Adjustment of the direct absorption determination was not necessary because recovery from the dermal dose was >90%. A value of 1% dermal absorption has been recommended as appropriate for use in risk assessment. This estimation takes into account any variability that would have likely occurred with testing several dose levels. The mouse single dose and rat single and multiple dose metabolism studies indicate that oral absorption is in the range of 90% or greater. Therefore, any extrapolation from the oral to the dermal route using the dermal absorption factor is not likely to grossly underestimate anticipated adverse effects.

3.2 FQPA Considerations

For a complete history of the FQPA considerations associated with clothianidin, refer to "Human

Health Risk Assessment for Clothianidin. Proposal for Tolerance of Residues in/on Pome Fruit and the Use on Tobacco, Turf, and Ornamental Plants" (D304499, W. Cutchin, 1/6/2005).

On November 14, 2002, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) evaluated the potential for increased susceptibility of infants and children from exposure to clothianidin as required by the Food Quality Protection Act (FQPA) of 1996. While no quantitative or qualitative susceptibility was observed in either of the developmental rat or rabbit studies, as discussed in section 3.1, quantitative susceptibility was observed in both the developmental neurotoxicity and reproduction rat studies. In the developmental neurotoxicity study, offspring toxicity (decreased body weight gains, motor activity, and acoustic startle response) was seen at a lower dose than the dose that caused maternal toxicity. However, HIARC determined that the degree of concern for the developmental neurotoxicity study is low and there are no residual uncertainties for pre- and/or postnatal toxicity because the observed effects are well characterized and there are clear NOAELs/LOAELs.

In the two-generation reproduction study, offspring toxicity (decreased body weight gains, delayed sexual maturation in males, decreased absolute thymus weights in F1 pups of both sexes, and an increase in stillbirths in both generations) was seen at a lower dose than the dose that caused parental toxicity. Based on evidence of decreased absolute and adjusted organ weights of the thymus and spleen in multiple studies in the clothianidin data base and on evidence of increased quantitative susceptibility of juvenile rats, compared to adults, in the two-generation reproduction study to these effects, the HIARC recommended that testing be conducted to assess immune system function in adults and in young animals following exposure during the period of organogenesis. Additionally, HIARC determined that there is insufficient data to justify selection of an additional safety factor for the protection of infants and children lower than the default value of 10X and that a UF_{DB} of 10X should be applied to both single and repeated dose exposure scenarios (*i.e.*, acute and chronic RfDs, short- and intermediate-term incidental oral exposures, and short-, intermediate-, and long-term dermal and inhalation exposures resulting from residential uses of clothianidin) to account for the lack of the developmental immunotoxicity study (DIT) with clothianidin. There are no residual uncertainties for pre- and/or postnatal toxicity for the two-generation reproduction study because the endpoint of concern is the one that is being used for short-, intermediate-, and long-term risk assessments and because an additional safety factor is applied for the lack of a DIT.

A guideline immunotoxicity study conducted in adult rats has now been reviewed by HED and shows no clothianidin-mediated immunotoxicity, in the form of a T-cell dependent anti-SRBC-forming cell response, in adults at doses lower than those resulting in generalized signs of toxicity (*e.g.*, decreases in body weight). While the antibody response was intact in adult rats in the presence of decreased lymphoid organ weights in this study, it cannot be concluded that offspring will respond similarly. A DIT study is required to evaluate the immune response of the offspring. Because results from the DIT could result in a more protective (*i.e.*, lower) regulatory endpoint, the 10X UF_{DB} is applied to account for the lack of this study (D318520, K. Schumacher, 10/17/2006).

In addition to the hazard data, the clothianidin risk assessment team evaluated the quality of the exposure data and found no residual uncertainties. The acute dietary exposure assessment is based on maximum residues of clothianidin observed in clothianidin and thiamethoxam field trials and assumes 100% crop treated (%CT). The chronic assessment is based on average residues from clothianidin and thiamethoxam field trials and also assumes 100% crop treated. For water, the highest acute estimate from conservative models was used for both the acute and the chronic dietary exposure analyses. By using these conservative assessments, acute and chronic exposures/risks will not be underestimated. The residential exposure assessment utilizes residential SOPs to assess post-application exposure to children as well as incidental oral ingestion by toddlers. The residential SOPs are based on reasonable worst-case assumptions and will not likely underestimate exposure/risk. These assessments are unlikely to underestimate the potential exposure to infants and children resulting from the use of clothianidin. Based on these data, the clothianidin risk assessment team concluded that no additional safety factor is needed to account for exposure considerations.

3.3 Hazard Identification and Toxicity Endpoint Selection

For a complete discussion of the endpoints, refer to "Human Health Risk Assessment for Clothianidin. Proposal for Tolerance of Residues in/on Pome Fruit and the Use on Tobacco, Turf, and Ornamental Plants" (D304499, W. Cutchin, 1/6/2005).

3.3.1 Acute Reference Dose (aRfD) - Females age 13-49

Study Selected: Developmental toxicity study in rabbits

MRID Number: 45422713

Dose and Endpoint for Establishing aRfD: 25 mg/kg/day (NOAEL), based on an increased litter incidence of a missing lobe of the lung observed at 75 mg/kg/day (LOAEL)

Uncertainty Factor(s): 1000X (10X for interspecies variability, 10X for intraspecies variability, 10X for database uncertainty)

Comments about Study/Endpoint/Uncertainty Factor:

The acute dietary endpoint for females in the 13 to 49 year age group is based on an increased litter incidence of a missing lobe of the lung. This developmental effect is presumed to occur following a single oral dose and is considered an appropriate endpoint for this population subgroup. Other effects observed at 75 mg/kg/day were premature deliveries, decreased gravid uterine weights and decreased litter average for ossified sternal centra per fetus; however, these are not considered to be single-dose effects.

3.3.2 Acute Reference Dose (aRfD) - General Population

Study Selected: Special neurotoxicity/pharmacology study in mice and rats

MRID Number: 45422823

Dose and Endpoint for Establishing aRfD: 25 mg/kg (NOAEL), based on transient signs of decreased spontaneous motor activity, tremors, and deep respirations observed at 50 mg/kg (LOAEL)

Uncertainty Factor(s): 1000X (10X for interspecies variability, 10X for intraspecies variability, 10X for database uncertainty)

Comments about Study/Endpoint/Uncertainty Factor:

The acute dietary endpoint for the general population is based on transient signs of decreased spontaneous motor activity, tremors and deep respirations in the mouse following a single oral dose. This endpoint is considered appropriate for the general population because the effects were observed following a single dose and the route of administration (oral) is appropriate for dietary considerations.

3.3.3 Chronic Reference Dose (cRfD)

Study Selected: Two-generation reproduction study in the rat

MRID Number: 45422714 through -16

Dose and Endpoint for Establishing cRfD: 9.8 mg/kg (NOAEL), based on decreased body weight gains and delayed sexual maturation, decreased absolute thymus weights in F1 pups, and an increase in stillbirths in both generations observed at 31.2 mg/kg (LOAEL)

Uncertainty Factor(s): 1000X (10X for interspecies variability, 10X for intraspecies variability, 10X for database uncertainty)

Comments about Study/Endpoint/Uncertainty Factor:

The chronic dietary endpoint is based on offspring effects in the two-generation reproduction study: decreased body weight gains and delayed sexual maturation, decreased absolute thymus weights in F1 pups, and an increase in stillbirths in both generations. This endpoint is considered appropriate for chronic dietary exposure because the route of administration (oral) is appropriate for dietary considerations. The study and endpoint were selected because they are protective of effects observed in all the other available studies.

3.3.4 Incidental Oral Exposure (Short- and Intermediate-Term)

Study Selected: Two-generation reproduction study in the rat

MRID Number: 45422714 through -16

Dose and Endpoint for Risk Assessment: 9.8 mg/kg (NOAEL), based on decreased body weight gains and delayed sexual maturation, decreased absolute thymus weights in F1 pups and an increase in stillbirths in both generations observed at 31.2 mg/kg (LOAEL)

Uncertainty Factor(s): 1000X (10X for interspecies variability, 10X for intraspecies variability, 10X for database uncertainty)

Comments about Study/Endpoint/Uncertainty Factor:

This endpoint is based on an oral study, which is the route of interest for an incidental oral risk estimate. The study and endpoint were selected because they are protective of effects observed in all the other available studies. The endpoint is appropriate for all durations, as the effect may be a result of either short- and/or longer-term exposure. In addition, it is appropriate for incidental oral exposure because it is based on offspring effects from the reproduction study.

3.3.5 Dermal Absorption

Dermal Absorption Factor: 1%

A dermal absorption study with monkeys is available. In a dermal penetration study (MRID 45868001), TI-435 [Clothianidin] as the FS 600 formulation (10% a.i.) [nitroimino- ^{14}C] TI-435) was administered to five male Rhesus monkeys. Test material was applied to a shaved area (4 cm x 6 cm) of skin on the back of each animal. The total dose was contained in 100 ml of test substance and was applied at a dose of 6.13 $\mu\text{g}/\text{cm}^2$. Animals were exposed for 8 hours, and then the application sites were washed. Subjects were monitored for 120 hours. Urine and feces were collected for the exposure period and the subsequent monitoring period.

3.3.6 Dermal Exposure (Short-, Intermediate- and Long-Term)

Study Selected: Two-generation reproduction study in the rat

MRID Number: 45422714 through -16

Dose and Endpoint for Risk Assessment: 9.8 mg/kg (NOAEL), based on decreased body weight gains and delayed sexual maturation, decreased absolute thymus weights in F1 pups and an increase in stillbirths in both generations observed at 31.2 mg/kg (LOAEL)

Uncertainty Factor(s): 1000X (10X for interspecies variability, 10X for intraspecies variability, 10X for database uncertainty)

Comments about Study/Endpoint/Uncertainty Factor:

This endpoint is based on an oral study. A dermal study is available; however, the selected endpoint addresses potential effects on offspring, which are not examined in the dermal study. Therefore, the study and endpoint were selected because they are protective of effects observed in all the available studies. The mouse single-dose and rat single- and multiple-dose metabolism studies indicate that oral absorption is in the range of 90% or greater. Therefore, extrapolation from the oral to the dermal route is not likely to grossly underestimate anticipated adverse effects. The endpoint is appropriate for all durations as the effect may be a result of either short- and/or longer-term exposure. A 1% dermal absorption factor should be used for route-to-route extrapolation.

3.3.7 Inhalation Exposure (Short-, Intermediate- and Long-Term)

Study Selected: Two-generation reproduction study in the rat

MRID Number: 45422714 through -16

Dose and Endpoint for Risk Assessment: 9.8 mg/kg (NOAEL), based on decreased body weight gains and delayed sexual maturation, decreased absolute thymus weights in F1 pups and an increase in stillbirths in both generations observed at 31.2 mg/kg (LOAEL)

Uncertainty Factor(s): 1000X (10X for interspecies variability, 10X for intraspecies variability, 10X for database uncertainty)

Comments about Study/Endpoint/Uncertainty Factor:

This endpoint is based on an oral study. No inhalation studies are available. Therefore, an oral study is selected to estimate risk using a route-to-route extrapolation. The study and endpoint were selected because it is protective of effects observed in all the available studies. The endpoint is appropriate for all durations as the effect may be a result of either short- and/or longer-term exposure. Absorption via inhalation is assumed to be equivalent to absorption via the oral route.

3.3.8 Level of Concern for Margin of Exposure

Table 3.3.8. Summary of Levels of Concern for Clothianidin Risk Assessment.			
Route	Short-Term (1 - 30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	100	100	100
Inhalation	100	100	100
Residential Exposure			
Dermal	1000	1000	1000
Inhalation	1000	1000	1000
Incidental Oral	1000	1000	1000

3.3.9 Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to a pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal, and inhalation exposures. The toxicity endpoints selected for these routes of exposure may be aggregated as follows: short-, intermediate- and long-term exposures (incidental oral, dermal, and inhalation exposure) can be aggregated because of the use of a common endpoint for oral, dermal (oral equivalent) and inhalation (oral equivalent) routes of exposure.

3.3.10 Classification of Carcinogenic Potential

In accordance with the Draft 1999 Carcinogen Risk Assessment Guidelines, the HIARC classified clothianidin as "not likely to be carcinogenic to humans." A statistical analysis showed that the increase in thyroid c-cell tumors in female rats was not significant, especially when carcinomas and adenomas are combined. The increased incidence of hepatocellular carcinomas in male rats at the low and high doses are just outside historical control incidences for the same testing laboratory (only 2 studies) but are within the historical control range for the animal supplier. In addition, there was no dose-response and there is no continuum (*i.e.* no preneoplastic lesions and no adenomas). Based on these factors, it was determined that there is no evidence of carcinogenicity in rats. There is no evidence of carcinogenicity in mice.

3.3.11 Summary of Toxicological Doses and Endpoints for Clothianidin for Use in Human Risk Assessments

Table 3.3.11a. Toxicological Doses and Endpoints for Clothianidin for Use in Dietary and Non-Occupational Human Health Risk Assessments.				
Exposure/Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects

Table 3.3.11a. Toxicological Doses and Endpoints for Clothianidin for Use in Dietary and Non-Occupational Human Health Risk Assessments.

Exposure/Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General Population, including Infants and Children)	NOAEL = 25 mg/kg/day	UF _A = 10x UF _H = 10x FQPA SF (UF _{DB}) = 10x	Acute RfD = 0.025 mg/kg/day aPAD = 0.025 mg/kg/day	Special neurotoxicity/pharmacology study in mice and rats LOAEL = 50 mg/kg based on transient signs of decreased spontaneous motor activity, tremors and deep respirations.
Acute Dietary (Females 13-49 years of age)	NOAEL = 25 mg/kg/day	UF _A = 10x UF _H = 10x FQPA SF (UF _{DB}) = 10x	Acute RfD = 0.025 mg/kg/day aPAD = 0.025 mg/kg/day	Developmental rabbit study LOAEL = 75 mg/kg/day based on an increased litter incidence of a missing lobe of the lung
Chronic Dietary (All Populations)	NOAEL = 9.8 mg/kg/day	UF _A = 10x UF _H = 10x FQPA SF (UF _{DB}) = 10x	Chronic RfD = 0.0098 mg/kg/day cPAD = 0.0098 mg/kg/day	Two-generation reproduction study LOAEL = 31.2 mg/kg/day based on decreased mean body weight gain and delayed sexual maturation, decreased absolute thymus weights in F1 pups and an increase in stillbirths in both generations.
Incidental Oral (All Durations)	NOAEL = 9.8 mg/kg/day	UF _A = 10x UF _H = 10x FQPA SF (UF _{DB}) = 10x	Residential LOC for MOE = 1000	Two-generation reproduction study LOAEL = 31.2 mg/kg/day based on decreased mean body weight gain and delayed sexual maturation, decreased absolute thymus weights in F1 pups and an increase in stillbirths in both generations.
Dermal (All Durations)	NOAEL = 9.8 mg/kg/day Dermal absorption rate = 17%	UF _A = 10x UF _H = 10x FQPA SF (UF _{DB}) = 10x	Residential LOC for MOE = 1000	Two-generation reproduction study LOAEL = 31.2 mg/kg/day based on decreased mean body weight gain and delayed sexual maturation, decreased absolute thymus weights in F1 pups and an increase in stillbirths in both generations.
Inhalation (All Durations)	NOAEL = 9.8 mg/kg/day Inhalation absorption rate = 100%	UF _A = 10x UF _H = 10x FQPA SF (UF _{DB}) = 10x	Residential LOC for MOE = 1000	Two-generation reproduction study LOAEL = 31.2 mg/kg/day based on decreased mean body weight gain and delayed sexual maturation, decreased absolute thymus weights in F1 pups and an increase in stillbirths in both generations.
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans"			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_{DB} = to account for the absence of key data (i.e., lack of a developmental immunotoxicity study). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern.

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Table 3.3.11b. Summary of Toxicological Doses and Endpoints for Clothianidin for Use in Occupational Human Health Risk Assessments.				
Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal (All Durations)	NOAEL=9.8 mg/kg/day Dermal absorption rate = 17%	UF _A =10x UF _H =10x	Occupational LOC for MOE = 100	Two-generation reproduction study LOAEL = 31.2 mg/kg/day based on decreased mean body weight gain and delayed sexual maturation, decreased absolute thymus weights in F1 pups and an increase in stillbirths in both generations.
Inhalation (All Durations)	NOAEL=9.8 mg/kg/day Inhalation absorption rate = 100%	UF _A =10x UF _H =10x	Occupational LOC for MOE = 100	Two-generation reproduction study LOAEL = 31.2 mg/kg/day based on decreased mean body weight gain and delayed sexual maturation, decreased absolute thymus weights in F1 pups and an increase in stillbirths in both generations.
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans"			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). MOE = margin of exposure. LOC = level of concern.

3.4 Endocrine disruption

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA has authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, clothianidin may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 Public Health and Pesticide Epidemiology Data

4.1 Incident Reports

There are currently no incident reports for clothianidin (H. Allender, 8/29/2006).

4.2 National Health and Nutritional Examination Survey (NHANES)

Clothianidin is not currently included in the NHANES database (R. Allen, 8/23/2006).

4.3 Agricultural Health Study (AHS)

Clothianidin is not currently included in the AHS database (R. Allen, 8/23/2006).

4.4 Other Pesticide Epidemiology Published Literature

No public health or epidemiology data were found for this chemical when the National Library of Medicine TOXNET and PubMed databases were searched (K. Schumacher, 9/20/2007).

5.0 Dietary Exposure/Risk Characterization

HED MARC Decision Memo (D282449, Y. Donovan, 4/25/2003)

HED Residue Chemistry Summary Document (D335355, W. Drew, **DRAFT**)

EFED Estimated Environmental Concentrations (D299401 and D301729, L. Liu, 7/6/2004)

HED Dietary Exposure Memo (D343102, W. Drew, **DRAFT**)

5.1 Pesticide Metabolism and Environmental Degradation

5.1.1 Metabolism in Primary Crops

Adequate plant metabolism studies are available reflecting the application of [¹⁴C]-clothianidin as a seed treatment to corn and sugar beets, as foliar applications to apples, and as soil and foliar applications to tomatoes. Based on these metabolism studies, HED concluded that the nature of the residue has been adequately delineated, and that parent only is the residue of concern (ROC) to be used in risk assessment and the tolerance expression for primary crops. However, HED also determined that future new uses on root crops and/or leafy vegetables will require analysis for residues of TMG along with parent in field trial samples. The metabolic profiles in the tested primary crops were similar, in that the highest level residue was the parent, clothianidin, with the exception of mature sugar beet tops.

5.1.2 Metabolism in Rotational Crops

Adequate confined and limited field rotational crop studies are available to support the proposed maximum use rate and proposed use directions on sugar beets. The metabolism of clothianidin in primary and rotational crops is similar. The MARC concluded that parent, TZNG, and MNG are the ROCs in rotational crops and that only parent needs to be included in the tolerance expression.

5.1.3 Metabolism in Livestock

The nature of clothianidin residues in livestock is adequately understood based on acceptable goat and hen metabolism studies. For ruminants, the MARC concluded that the ROCs for risk assessment include parent and the metabolites TZU, TZG, TZNG, and ATMG-Pyruvate; for poultry, the MARC concluded that the ROCs for risk assessment include parent and the metabolites TZU, TZG, TZNG, and ATG-Acetate. However, for purposes of tolerances, the MARC recommended that only parent needs to be included in the tolerance expression.

5.1.4 Analytical Methodology

Adequate LC/MS/MS methods are available for both collecting data and enforcing tolerances for clothianidin residues in plant (Bayer Methods 00552 and 109240-1) and animal (Bayer Method 00624) commodities. The validated limit of quantitation (LOQ) for clothianidin in plant commodities is 0.010 ppm, except for wheat straw (0.020 ppm), and the validated LOQs are 0.010 ppm in milk and 0.020 ppm in animal tissues. All three of these methods have been reviewed by BEAD's Analytical Chemistry Laboratory (ACL), approved for tolerance enforcement, and forwarded to FDA for inclusion in PAM Volume II.

In the current sugar beet field trials and processing studies, residues of clothianidin and its metabolite, TMG, were determined in each commodity using an LC/MS/MS method (Bayer Method TI-002-P05-001). This method is similar to the enforcement methods, but it also determines residues of TMG. For this method, residues are extracted sequentially with acetonitrile (ACN) and ACN/water, then fortified with [$^2\text{H}_6$]-internal standards of clothianidin and TMG. Residues are then acidified, purified using a C_{18} solid-phase extraction (SPE) cartridge, and determined by LC/MS/MS. Residues of clothianidin and TMG are expressed in clothianidin equivalents. The method was adequately validated in conjunction with the analysis of study samples. The validated LOQ for both clothianidin and TMG is 0.010 ppm in sugar beet roots, tops, and processed fractions, with the exception of clothianidin in molasses (0.020 ppm). The statistically calculated limits of detection (LODs) for clothianidin are 0.003 ppm in roots, tops, refined sugar, and dried pulp, and 0.011 ppm in molasses. The statistically calculated LODs for TMG are 0.001 ppm in roots, 0.002 ppm in refined sugar and dried pulp, 0.003 ppm in tops, and 0.005 ppm in molasses.

Multiresidue method testing of clothianidin and its metabolites MNG, TZG, TZNG, TZU, and ATMG-Pyr have been submitted (D282446, Y. Donovan, 5/1/2003). However, it was determined that clothianidin and its major metabolites are not adequately recovered using any of the multiresidue methods. These data were forwarded to the US FDA for further evaluation.

5.1.5 Environmental Degradation

The fate and disposition of clothianidin in the environment suggest that it is persistent and mobile, stable to hydrolysis, and has potential to leach to ground water, as well as runoff to surface waters. The high persistence of clothianidin (aerobic soil metabolism and terrestrial field

dissipation half-lives ranging from half a year to several years) may cause accumulation of the chemical in soils following repeated uses.

5.1.6 Pesticide Metabolites and Degradates of Concern

Table 5.1.6. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression.

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Parent (For Sugar Beet Tops only: Parent and TMG ¹)	Parent
	Rotational Crop	Parent, TZNG, MNG	Parent
Livestock	Ruminant	Parent, TZU, TZG, TZNG, ATMG-Pyr	Parent
	Poultry	Parent, TZU, TZG, TZNG, ATG-Ac	Parent
Drinking Water		Parent	Not Applicable

¹ Although TMG is a residue of concern to include in risk assessment for sugar beet tops, this is no longer a regulated food or significant feed item.

5.1.7 Drinking Water Residue Profile

EFED provided Tier I Estimated Drinking Water Concentrations (EDWCs) for clothianidin in surface water and in ground water for use in human health risk assessments. The simulation model FIRST was used to calculate the surface water EDWCs, and the SCI-GROW model was used to calculate the groundwater EDWC. No clothianidin monitoring data were available. Although clothianidin is a major metabolite of thiamethoxam in plants and in animals, it was not found in thiamethoxam environmental fate studies. Therefore, exposure to clothianidin in drinking water due to thiamethoxam uses is not expected. The MARC's decision on residues of concern for thiamethoxam in drinking water is parent only. For the simulation models, the application rate of 0.4 lbs a.i./A for turfgrass was used. This rate is the highest of all the proposed and existing uses. The EDWCs for clothianidin in surface waters are 7.29 ppb for acute risk calculations and 1.35 ppb for chronic risk and cancer risk calculations. Clothianidin EDWCs in groundwater are not expected to exceed 5.84 ppb. Typically, HED uses the higher of the surface or groundwater estimates for each duration when assessing dietary risk (e.g., 7.29 ppb from surface water for acute exposures and 5.84 ppb from groundwater for chronic exposures). As an added conservatism in this chronic assessment, the acute 7.29 ppb EDWC from surface water was used for both the acute and chronic analyses.

Table 5.1.7. Summary of Estimated Surface Water and Groundwater Concentrations for Clothianidin.

	Surface Water Conc., ppb ^a	Groundwater Conc., ppb ^b
Acute	7.29	5.84
Chronic (non-cancer)	1.35	5.84

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Table 5.1.7. Summary of Estimated Surface Water and Groundwater Concentrations for Clothianidin.		
	Surface Water Conc., ppb ^a	Groundwater Conc., ppb ^b
Chronic (cancer)	N/A	N/A
^a From the Tier 1 FIRST model assuming a maximum applicator rate of 0.4 lb a.i./A, a K _{oc} of 84, and a soil aerobic metabolic half-life of 744 days.		
^b From the SCI-GROW model.		

5.1.8 Food Residue Profile

The sugar beet field trial data are adequate and support the proposed use pattern. Adequate numbers of trials were conducted in the appropriate geographical regions, and samples were analyzed for both ROCs using an adequate method. Provided that the storage stability data for TMG in sugar beet leaves and potatoes are submitted and deemed adequate, the sample storage conditions and durations are also supported by the available storage stability data. The clothianidin residue data support the proposed 0.02 ppm tolerance for sugar beet roots. Although residue data were also submitted for sugar beet tops, the Agency no longer considers sugar beet tops to be a significant livestock feedstuff; therefore, a separate tolerance for tops is not required.

Residue data from the available limited field rotational crop studies, conducted at 0.144-0.171 lb ai/A (1.5-1.8X the proposed rate for sugar beets), adequately support the current tolerances for inadvertent residues in selected rotational crops.

Provided that the supporting storage stability data are submitted, the sugar beet processing study is adequate. The results from the sugar beet processing study indicate that a separate tolerance is not required in refined sugar, as clothianidin residues did not concentrate in sugar (<0.3X). However, clothianidin residues concentrated by 1.5X in dried pulp and by 2.9X in molasses. The maximum possible processing factor for sugar beet dried pulp is 20X. Based on HAFT residues of 0.017 ppm for clothianidin in sugar beet roots and the empirical processing factors, the maximum expected residues would be 0.026 ppm in dried pulp and 0.049 ppm in molasses. These data would support tolerances of 0.03 ppm in dried pulp and 0.05 ppm in molasses.

Tolerances for clothianidin residues in animal commodities were recently reassessed in conjunction with petitions for uses on grapes, potatoes, sorghum, and cotton (D309473; William Drew; 2/1/2006). As the proposed sugar beet tolerances do not alter the theoretical dietary burden of livestock for clothianidin residues, reassessment of animal tolerances is not required for this petition, and the current tolerance in milk is adequate.

5.1.9 International Residue Limits

Regarding international MRLs for clothianidin, harmonization of the proposed tolerances for sugar beet roots, molasses, and dried pulp is not an issue; as of September 2007, there are no established or proposed Canadian, Mexican, or Codex MRLs for clothianidin residues on sugar beet commodities.

5.2 Dietary Exposure and Risk

HED Dietary Exposure Memo (D343102, W. Drew, DRAFT)

Acute and chronic dietary exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.03). Clothianidin has been classified as "not likely" carcinogenic; therefore, cancer risk from exposure to clothianidin is not of concern. Clothianidin is a major metabolite of the active ingredient thiamethoxam and residues of clothianidin coming from thiamethoxam were accounted for in these assessments. All registered, pending, and proposed uses of thiamethoxam, as of the date of this memorandum, are included in these assessments. The acute assessment is based on maximum residues of clothianidin observed in clothianidin and thiamethoxam field trials and assumes 100% crop treated (%CT). The chronic assessment is based on average residues from clothianidin and thiamethoxam field trials and also assumes 100% crop treated. For crops that are registered for both thiamethoxam and clothianidin, residues were estimated by combining values from both sources of clothianidin. Assuming 100% crop treated in these analyses results in a potential "double counting" of clothianidin coming from thiamethoxam for crops that have registered uses of both compounds, since the label for clothianidin does not permit application of another "Group 4A" insecticide (e.g., thiamethoxam) following application of clothianidin. Therefore, this method of accounting for thiamethoxam's involvement in clothianidin exposure likely overestimates that particular contribution to total exposure. The empirical processing factor for apple juice is used for apple and pear juice, and empirical factors were used for grape juice, raisins, and sugar beet molasses; otherwise, DEEM default processing factors are used. The analyses include direct incorporation of estimated clothianidin residues in drinking water. For water, the highest acute estimate from conservative models was used for both the acute and the chronic dietary exposure analyses.

Based on these highly conservative assumptions, acute dietary risk estimates at the 95th percentile of exposure are less than or equal to 45% of the acute population-adjusted dose (aPAD) for all population subgroups. Children 1 to 2 years of age were the most highly exposed subgroup, utilizing 45% of the aPAD, while the general US population utilized 11% of the aPAD. Chronic dietary risk estimates are less than or equal to 16% of the chronic population-adjusted dose (cPAD) for all population subgroups. Children 1 to 2 years of age were again the most highly-exposed subgroup, utilizing 16% of the cPAD, while the general US population utilized 5% of the cPAD. Generally, HED is concerned when risk estimates exceed 100% of the PAD; therefore, all acute and chronic dietary risk estimates are below HED's level of concern (LOC).

5.2.1 Acute Dietary Exposure/Risk

Table 5.2.1. Summary of the Acute Dietary Exposure and Risk Estimates for Clothianidin.			
Population Subgroup	Acute PAD (mg/kg/day)	Acute Estimates (95 th Percentile)	
		Dietary Exposure (mg/kg/day)	% aPAD
General U.S. Population	0.025	0.002813	11
All Infants (< 1 year old)	0.025	0.007806	31
Children 1-2 years old	0.025	0.011227	45
Children 3-5 years old	0.025	0.007231	29
Children 6-12 years old	0.025	0.003085	12
Youth 13-19 years old	0.025	0.001403	6

Table 5.2.1. Summary of the Acute Dietary Exposure and Risk Estimates for Clothianidin.			
Population Subgroup	Acute PAD (mg/kg/day)	Acute Estimates (95 th Percentile)	
		Dietary Exposure (mg/kg/day)	% aPAD
Adults 20-49 years old	0.025	0.001902	8
Adults 50+ years old	0.025	0.002102	8
Females 13-49 years old	0.025	0.001975	8

5.2.2 Chronic Dietary Exposure/Risk

Table 5.2.2. Summary of the Chronic Dietary Exposure and Risk Estimates for Clothianidin.							
Population Subgroup	Chronic PAD (mg/kg/day)	Source of Clothianidin					
		Clothianidin		Thiamethoxam		Total	
		Dietary Exposure (mg/kg/day)	% cPAD	Dietary Exposure (mg/kg/day)	% cPAD	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.0098	0.000368	4	0.000105	1	0.000473	5
All Infants (< 1 year old)	0.0098	0.001083	11	0.000179	2	0.001262	13
Children 1-2 years old	0.0098	0.001315	13	0.000263	3	0.001578	16
Children 3-5 years old	0.0098	0.000921	9	0.000223	2	0.001144	12
Children 6-12 years old	0.0098	0.000447	5	0.000142	2	0.000589	6
Youth 13-19 years old	0.0098	0.000222	2	0.000095	1	0.000317	3
Adults 20-49 years old	0.0098	0.000273	3	0.000084	1	0.000357	4
Adults 50+ years old	0.0098	0.000300	3	0.000085	1	0.000385	4
Females 13-49 years old	0.0098	0.000279	3	0.000081	1	0.000360	4

5.3 Anticipated Residue and Percent Crop Treated (%CT) Information

The acute assessment is based on maximum residues of clothianidin observed in clothianidin and thiamethoxam field trials and assumes 100% crop treated. The chronic assessment is based on average residues from clothianidin and thiamethoxam field trials and also assumes 100% crop treated. For crops that are registered for both thiamethoxam and clothianidin, maximum field-trial residues (acute assessment) or average field trial residues (chronic assessment) were combined for each crop (*i.e.*, clothianidin from clothianidin field trials + clothianidin from thiamethoxam field trials).

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

HED Occupational/Residential Exposure Memo, (D296176, M. Dow, 2/24/2004)

HED Occupational/Residential Exposure Memo, (D340131, S. Oonnithan, 6/28/2007)

Residential (non-occupational) exposure to clothianidin results solely from currently registered use of this compound, with no additional residential exposure expected from the proposed new use on sugar beet seeds. Refer to the risk assessment for use on turfgrass (D304499, W. Cutchin, 1/6/2005) or to the corresponding residential exposure assessment (D296176, M. Dow, 2/24/2004) for more details.

Subsequent to the risk assessment on the residential exposure to clothianidin, thiamethoxam has been registered for use on turf. Because the actions of these compounds are similar and because the thiamethoxam label recommends against the application of another Group 4A insecticide, it is highly unlikely that turf would be treated with thiamethoxam and clothianidin simultaneously. Since the duration of residential exposure to either compound is short-term, simultaneous exposure to clothianidin from both sources is highly unlikely. Residential exposure to clothianidin applied directly on turf is expected to be higher than exposure to clothianidin residues when thiamethoxam is applied on turf, so previously calculated risks for the use of clothianidin, *per se*, on turf are considered protective of residential exposure to clothianidin as either an active ingredient or a metabolite of thiamethoxam.

6.1 Residential Handler Exposure

Although residential handler exposure is not expected from the currently registered or proposed uses of clothianidin, due to the absence of products registered or proposed for homeowner use, the exposure estimates in Table 6.2 do include adult exposure from application with a granular push-type spreader. Therefore, this represents an overestimate of total exposure.

6.2 Residential Post-application Exposure

Based on the registered use patterns on turfgrasses, a number of residential or recreational post-application exposures are possible. In a residential setting, a "homeowner" may be exposed during application of the material to his or her lawn (although not in the case of clothianidin, due to the absence of products registered or proposed for homeowner use). Further, the "homeowner" may also experience post-application dermal exposure. Toddlers may be exposed via "hand-to-mouth" oral exposures and/or dermal exposures. These estimated exposures and risks are also presented. "Aggregated" exposures are presented for toddlers (*i.e.*, hand-to-mouth turf + hand-to-mouth soil + dermal post-application). Hand-to-mouth ingestion of granules is considered episodic in nature, that is, a "one-time" event. Therefore the exposure from ingestion of granules is not combined with believed multiple exposures from "mouthing" of turf or soil or from post-application dermal exposure. Golfers may be exposed to post-application residues, and estimates of adult and adolescent golfer exposures are presented.

It is HED's policy to routinely conduct screening level assessments (based on standard values in the Residential SOPs) for children's incidental ingestion of granules, when a granular pesticide may be applied in residential settings. The screening-level assessment for clothianidin resulted in an MOE of 250 and is a risk of concern. Based on information provided by Arysta (email from Doina Bujor dated 11/27/2006) on the particle volumes of the granular clothianidin formulations, HED agrees that there is little exposure potential for children's incidental ingestion of clothianidin granules. The particle size is relatively small, and if used according to label directions, it is unlikely that clothianidin granules would be accessible to a child.

The MOEs for the residential post-application exposures/risks range from 1,300 to 490,000 (Table 6.2). MOE values greater than 1000 are considered adequate to protect adults and children from residential post-application exposures to clothianidin. The estimated MOEs are based upon conservative assumptions and are >1000; therefore, the estimated risks from

residential post-application exposures do not exceed HED's level of concern.

Table 6.2. Summary of Residential Exposure and Risk Estimates for Clothianidin.		
Activity	Exposure (mg a.i./kg bw/day)	MOE
Toddler oral hand to mouth from contacting treated turf	0.0059	1700
Toddler incidental oral ingestion of treated soil	0.00002	490000
Adult dermal post applic turf contact	0.00108	9100
Adult combined dermal exposure = application + postapplication	application 0.000026 post-application + 0.00108	8900
Toddler dermal post applic turf contact	0.00155	6300
Toddler combined oral (except granules) and dermal exposures	treated turf + treated soil + dermal 0.00747	1300
Adult golfer post app turf contact	0.000075	130000
Child golfer post app turf contact	0.000128	77000

6.3 Other (Spray Drift, etc.)

Spray drift is a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for clothianidin. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. On a chemical by chemical basis, the Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

6.4 Exposure from Use of Tobacco

Exposure to clothianidin from use of tobacco has been addressed in a previous risk assessment (D304499, W. Cutchin, 1/6/2005) and is not re-examined in this document.

7.0 Aggregate Risk Assessments and Risk Characterization

In accordance with the FQPA, HED must consider and aggregate pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from dietary and residential sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

Short- and intermediate-term aggregate risk assessment is required for clothianidin due to potential residential and/or recreational exposures to residues on turfgrass.

7.1 Acute Aggregate Risk

Estimates of pesticide residues in drinking water were incorporated directly into the dietary exposure analysis to assess aggregate acute risk. Therefore, the acute aggregate risk estimates are equivalent to the acute dietary risk estimates provided in Table 5.2.1. The acute aggregate risks associated with the registered and proposed uses of clothianidin do not exceed HED's level of concern for the general U.S. population or any population subgroup.

7.2 Short- and Intermediate-Term Aggregate Risk

The HIARC has determined that, for clothianidin, the toxicological effects are the same across oral, dermal, and inhalation routes of exposure and has selected the same endpoint and dose for short- and intermediate-term exposure scenarios. Therefore, the exposures are simply summed (combined/aggregated) for use in risk calculations. Short- and intermediate aggregate risk estimates range from an MOE of 1,100 for toddlers (food + water + treated turf + treated soil + dermal) to 22,000 for youth golfers (food + water + post-application treated turf). The short- and intermediate-term aggregate risks associated with the registered and proposed uses of clothianidin do not exceed HED's level of concern for the general U.S. population or any population subgroup.

Population	NOAEL (mg/kg/day)	LOC ¹	Average Food & Water Exposure (mg/kg/day)	Residential Exposure ² (mg/kg/day)	Aggregate MOE [food, water, and residential] ³
Toddler	9.8	1000	0.001578	0.007470	1100
Females 13-49	9.8	1000	0.000360	0.001106	6700
Adult (male)	9.8	1000	0.000473	0.001106	6200
Adult golfer	9.8	1000	0.000473	0.000075	18000
Youth golfer	9.8	1000	0.000317	0.000128	22000

¹ The Level of Concern is based on the following uncertainty factors: 10X for interspecies variability, 10X for intraspecies variability, and 10X for database uncertainty for the lack of a developmental immunotoxicity study.

² Residential Exposure = [oral exposure + dermal exposure + inhalation exposure]. See Table 6.2.

³ Aggregate MOE = [NOAEL / (Avg Food & Water Exposure + Residential Exposure)]

7.3 Long-Term Aggregate Risk

Long-term residential exposure to clothianidin (*i.e.*, >6 months) is not considered likely to occur. Estimates of pesticide residues in drinking water were incorporated directly into the dietary exposure analysis to assess aggregate chronic risk. Therefore, the long-term aggregate risk estimates are equivalent to the chronic dietary risk estimates provided in Table 5.2.2. As previously noted, clothianidin is a metabolite of the active ingredient thiamethoxam and

exposures to clothianidin due to thiamethoxam uses were considered in the chronic dietary assessment. The long-term aggregate risks associated with clothianidin exposure resulting from the registered and proposed uses of clothianidin and from the registered uses of thiamethoxam do not exceed HED's level of concern for the general U.S. population or any population subgroup.

7.4 Cancer Risk

Clothianidin has been classified by HED HIARC as a "not likely human carcinogen." As such, cancer risk from clothianidin is not of concern to HED.

8.0 Cumulative Risk Characterization/Assessment

Clothianidin is a member of the neonicotinoid class of pesticides and is a metabolite of another neonicotinoid, thiamethoxam. Structural similarities or common effects do not constitute a common mechanism of toxicity. Evidence is needed to establish that the chemicals operate by the same, or essentially the same sequence of major biochemical events (EPA, 2002). Although clothianidin and thiamethoxam bind selectively to insect nicotinic acetylcholine receptors (nAChR), the specific binding site(s)/receptor(s) for clothianidin, thiamethoxam, and the other neonicotinoids are unknown at this time. Additionally, the commonality of the binding activity itself is uncertain, as preliminary evidence suggests that clothianidin operates by direct competitive inhibition, while thiamethoxam is a non-competitive inhibitor. Furthermore, even if future research shows that neonicotinoids share a common binding activity to a specific site on insect nicotinic acetylcholine receptors, there is not necessarily a relationship between this pesticidal action and a mechanism of toxicity in mammals. Structural variations between the insect and mammalian nAChRs produce quantitative differences in the binding affinity of the neonicotinoids towards these receptors, which, in turn, confers the notably greater selective toxicity of this class towards insects, including aphids and leafhoppers, compared to mammals. While the insecticidal action of the neonicotinoids is neurotoxic, the most sensitive regulatory endpoint for clothianidin is based on unrelated effects in mammals, including changes in body and thymus weights, delays in sexual maturation, and still births. Additionally, the most sensitive toxicological effect in mammals differs across the neonicotinoids (e.g., testicular tubular atrophy with thiamethoxam; mineralized particles in thyroid colloid with imidaclopid). Thus, there is currently no evidence to indicate that neonicotinoids share common mechanisms of toxicity, and EPA is not following a cumulative risk approach based on a common mechanism of toxicity for the neonicotinoids. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism released by EPA's Office of Pesticide Programs on EPA's website at <http://www.epa.gov/pesticides/cumulative/>.

Note that because clothianidin is a major metabolite of thiamethoxam, EPA has combined exposure to clothianidin resulting both from thiamethoxam use and from use of clothianidin as an active ingredient and has compared this aggregate exposure estimate to relevant endpoints for

clothianidin. For agricultural uses, EPA has taken the further conservative step of assuming that, in instances where both thiamethoxam and clothianidin are registered for use on a crop, both pesticides will, in fact, be used on that crop in the same growing season, despite resistance-management labeling to the contrary.

9.0 Occupational Exposure/Risk Pathway

HED Occupational/Residential Exposure Memo, (D340131, S. Oonnithan, 6/28/2007)

Poncho Beta (EPA File Symbol: 264-RNLA), a new flowable concentrate containing 34.3% clothianidin (3.33 lb ai/gal) and 4.6% *beta*-cyfluthrin (0.44 lb ai/gal) as active ingredients, is proposed for the seed treatment of sugar beets to control early season insect pests. The petitioner is proposing to treat sugar beet seeds with undiluted Poncho Beta in a commercial facility using liquid or slurry coating equipment at the rate of 5.07 fl. oz. of product per 1 unit of sugar beet seeds, amounting to 0.032 lb ai/lb of seed. The treated seeds are bagged and stored until used.

The petitioner has not submitted any product-specific exposure data for estimating the risk to handlers; therefore, the default values from HED's generic databases, such as Pesticide Handlers Exposure Database (PHED) and Science Advisory Committee on Exposure (ExpoSAC) Policies were used to calculate the occupational exposures to loaders, applicators, and other seed treatment (ST) workers.

9.1 Short- and Intermediate-Term Handler Risk

The treatment of sugar beet seeds may last more than a month due to the longer planting season; therefore, both short-term (1-30 days) and intermediate-term (1-6 months) occupational exposures were assessed. The liquid Poncho Beta formulation is used without any dilution, and the ST process is expected to result in the following exposure scenarios:

- loader/treater who transfers the formulation and treats the seeds (in some ST scenarios, loading and treating may be performed by the same or separate individuals)
- bagger of treated seeds
- sewer of bags containing treated seeds
- workers doing multiple activities (in a small ST setup, all the operations may be performed by the same worker).

Summaries of the handler exposures/risks from sugar beet seed treatment are presented in Table 9. Since the NOAELs for the dermal and inhalation routes of exposure and durations of exposure are the same, the total MOEs (Table 9) represent both the short- and intermediate-term risks. A total MOE of 100 or more is sufficient to protect workers from all of the occupational handler exposures to clothianidin. Risk estimates calculated for the seed treatment handlers are below the level of concern for all workers who wear baseline PPE (MOEs = 170 to 1400), with the highest risk for those workers who do multiple operations on a daily basis. Use of chemical resistant gloves and dust/mist respirators, which is a label requirement for all workers involved in ST of sugar beet seeds, is expected to provide additional protection from exposure to the pesticide active ingredients in Poncho Beta.

9.2 Short-Term Post-application Risk

It is assumed that the sugar beet planting season may last more than 30 days/year, resulting in both short- and intermediate-term post-application exposures. However, because the dermal toxicity doses (NOAELs) are the same for short- and intermediate-term exposures, the MOEs are also the same for both exposure durations.

The postapplication exposure to clothianidin is likely while farm workers transfer the treated seed from bags to planter-hopper and while planting/drilling the seed. HED has determined that the handling and planting of treated sugar beet seeds involve negligible exposure as long as the treated seeds are not contacted directly. A likely exposure scenario for planters handling and planting treated seeds indicated that the risk is not of concern. Additionally, the label requires handlers of Poncho Beta seed bags that were treated prior to planting to wear basic PPE, which should further minimize any dermal exposure to clothianidin. Even though no PPE is recommended for planters while seeding/planting, no direct contact with treated seed is expected, as the planting machinery places/drills the seed and covers it with soil, doing both steps in one operation. Covering treated seeds with soil protects workers who may reenter a field soon after planting for irrigation. No other postapplication activity is performed in a freshly seeded sugar beet field. There is no restricted entry interval (REI) for treating and planting of pre-treated seeds as REI is not applicable for ST operations.

The handler and postapplication risks estimated in this assessment are assumed to be representative of high-end exposures. The exposures for handlers and farmers are based on a central tendency estimate of unit exposure and an upper-percentile assumption for the application rate. The uncertainties associated with this assessment stem from the assumptions regarding the amount of chemical handled and the amount of seed treated/planted per day. The estimated exposures are believed to be reasonable high-end estimates based on observations from field studies and professional judgment.

An MOE of 100 or more is sufficient to protect workers from post-application occupational exposures to clothianidin. The post-application risk estimate for sugar beet seed planters is below the level of concern at the baseline level (MOE = 4,800). This estimate is presented in Table 9.

Table 9. Short- and Intermediate-Term Risks to Workers and Planters Resulting From the Seed Treatment of Sugar Beet with Poncho Beta Containing Clothianidin.

Exposure Scenarios	PPE ¹	Qty Treated or Planted/day (lbs)	Unit Exp. Dermal/day (mg/lb ai)	Unit Exp. Inhal./day (µg/lb ai)	Dermal Dose/day (mg/kg) ²	Inhal. Dose/day (mg/kg) ²	Total MOE ³
Treatment:							
Loading/Treating	S, G	52,000	0.023	0.34	0.00644	0.00952	610
Bagging, treated seed	S	52,000	0.0091	0.16	0.00255	0.00448	1,400
Sewing, bagged seed	S	52,000	0.0062	0.23	0.00174	0.00644	1,200
Doing multiple jobs	S, G	52,000	0.0420	1.6	0.01176	0.04479	170
Post-treatment:							
Planting of treated seeds	S #	640	0.25	3.4	0.00086	0.00117	4,800

1. S = Single layer (long sleeve shirt and long pants) and no gloves, G = chemical resistant gloves.

2. Dermal dose = [unit dermal exposure * dermal absorption (%/100) * application rate * area treated/day] / body weight.

Inhalation dose = [unit exposure * (µg/1000) mg conversion factor * dermal absorption (%/100) * application rate * area treated/day] / body weight.

3. Total MOE = NOAEL / (Dermal dose + Inhalation dose). Total MOE represents both the short- and intermediate-term risks.

#. For handlers/planters, gloves are to be used for loading only.

10.0 Data Needs and Label Recommendations

10.1 Toxicology

Developmental immunotoxicity study

10.2 Residue Chemistry

To support the stability of TMG residues in sugar beet commodities, the petitioner cited data from an ongoing study examining the stability of TMG in frozen sugar beet leaves, and potato tubers, flakes, and chips. These data should be submitted for evaluation.

10.3 Occupational and Residential Exposure

None

References:

HED Clothianidin Risk Assessment (D304499, W. Cutchin, 1/6/2005)
HED DIT Waiver Request Memo (D318520, K. Schumacher, 10/17/2006)
HED MARC Decision Memo (D282449, Y. Donovan, 4/25/2003)
HED Residue Chemistry Summary Document ((D335355, W. Drew, 10/16/2007)
EFED Estimated Environmental Concentrations (D299401 and D301729, L. Liu, 7/6/2004)
HED Dietary Exposure Memo (D343102, W. Drew, 10/16/2007)
HED Occupational/Residential Exposure Memo, (D340131, S. Oonnithan, 6/28/2007)
HED Occupational/Residential Exposure Memo, (D296176, M. Dow, 2/24/2004)

Appendix A: Toxicology Assessment

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for food uses for clothianidin are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Test	Technical	
	Required	Satisfied
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (rodent)	yes	yes
870.3150 Oral Subchronic (nonrodent)	yes	yes
870.3200 21-Day Dermal	yes	yes
870.3250 90-Day Dermal	no	-
870.3465 90-Day Inhalation	no	-
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (nonrodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent)	yes	yes
870.4100b Chronic Toxicity (nonrodent)	yes	yes
870.4200a Oncogenicity (rat)	yes	yes
870.4200b Oncogenicity (mouse)	yes	yes
870.4300 Chronic/Oncogenicity	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5xxx Mutagenicity—Structural Chromosomal Aberrations ..	yes	yes
870.5xxx Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a Acute Delayed Neurotox. (hen)	no	-
870.6100b 90-Day Neurotoxicity (hen)	no	-
870.6200a Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b 90-Day Neuro. Screening Battery (rat)	yes	yes
870.6300 Develop. Neuro	yes	yes
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	yes	yes
Special Studies		
Developmental Immunotoxicity	yes	no

A.2 Toxicity Profiles

Table A.2.1 Acute Toxicity Profile - Clothianidin Technical, Intermediates, and Metabolites					
Test Material	Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
Technical	870.1100	Acute oral - rat	45422621	LD ₅₀ > 5000 mg/kg	IV
BN0230M <i>Metabolite</i>	870.1100	Acute oral - rat	45422628	LD ₅₀ > 2000 mg/kg (♂+♀)	III
BN0335E2 <i>Metabolite</i>	870.1100	Acute oral - rat	45422623	LD ₅₀ > 2000 mg/kg (♂+♀)	III
MAI <i>Metabolite</i>	870.1100	Acute oral - rat	45422629	LD ₅₀ = 758 mg/kg (♀) Males not more susceptible	III
Clothianidin-CCMT-Adduct <i>Intermediate</i>	870.1100	Acute oral - rat	45422630	LD ₅₀ > 2000 mg/kg (♂+♀)	III
Clothianidin-Hexahydropyrimidine <i>Intermediate</i>	870.1100	Acute oral - rat	45422631	LD ₅₀ > 2000 mg/kg (♂+♀)	III
Clothianidin-Triazan <i>Intermediate</i>	870.1100	Acute oral - rat	45422632	LD ₅₀ > 2000 mg/kg (♂+♀)	III
TMG <i>Metabolite</i>	870.1100	Acute oral - rat	45422625	LD ₅₀ < 550 mg/kg (♂) LD ₅₀ = 567 mg/kg (♀)	II
TZMU <i>Metabolite</i>	870.1100	Acute oral - rat	45422624	LD ₅₀ = 1424 mg/kg (♂) LD ₅₀ = 1282 mg/kg (♀)	III
TZNG <i>Metabolite</i>	870.1100	Acute oral - rat	45422626	LD ₅₀ > 1450 mg/kg (♂) LD ₅₀ = 1481 mg/kg (♀)	III
Technical	870.1100	Acute oral - mouse	45422622	LD ₅₀ = 389 mg/kg (♂; 95% C.I. = 380-475) LD ₅₀ = 465 mg/kg (♀; 95% C.I. = 384-561) LD ₅₀ = 425 mg/kg (♂+♀; 95% C.I. = 380-475)	II
Technical	870.1200	Acute dermal - rat	45422634	LD ₅₀ > 2000 mg/kg	III
Technical	870.1300	Acute inhalation	45422636	LC ₅₀ > 5.538 mg/L (♂+♀)	IV
Technical	870.2400	Acute eye irritation	45422701	Slightly irritating to the eye	IV
Clothianidin-CCMT-Adduct <i>Intermediate</i>	870.2400	Acute eye irritation	45422814	Not irritating to the eye	IV
Clothianidin-Triazan <i>Intermediate</i>	870.2400	Acute eye irritation	45422819	Not irritating to the eye	IV
Technical	870.2500	Acute dermal irritation	45422703	Not irritating to the skin	IV
Clothianidin-CCMT-Adduct <i>Intermediate</i>	870.2500	Acute dermal irritation	45422813	Not irritating to the skin	IV
Clothianidin-Triazan <i>Intermediate</i>	870.2500	Acute dermal irritation	45422820	Not irritating to the skin	IV
Technical	870.2600	Skin sensitization	45422705	Is not a sensitizer under conditions of study	N/A
Clothianidin-CCMT-Adduct <i>Intermediate</i>	870.2600	Skin sensitization	45422815	Is not a sensitizer under conditions of study	N/A
Clothianidin-Triazan <i>Intermediate</i>	870.2600	Skin sensitization	45422821	Is a sensitizer under conditions of study	N/A

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile		
Guideline No.	Study Type	Results
870.3100	90-Day oral toxicity - rat	NOAEL = 27.9/34.0 mg/kg/day (M/F) LOAEL = 202.0/254.2 mg/kg/day (M/F) based on decreased BW and BW gain.
870.3150	90-Day oral toxicity - dog	NOAEL = 19.3/42.1 mg/kg/day (M/F) LOAEL = 40.9/61.8 mg/kg/day (M/F) based on thinness, decreased body weight, body weight gain and anemia (1 M); and on decreased white blood cells, albumin, and total protein (F).
870.3200	21/28-Day dermal toxicity - rat	NOAEL = 1000 mg/kg/day (HDT) LOAEL = Not established
870.3700a	Prenatal developmental in rodents - rat	Maternal NOAEL = 10 mg/kg/day Maternal LOAEL = 40 mg/kg/day based on decreased body weight gain and food consumption. Developmental NOAEL = 125 mg/kg/day (HDT) Developmental LOAEL = Not established
870.3700b	Prenatal developmental in nonrodents - rabbit	Maternal NOAEL = 25 mg/kg/day Maternal LOAEL = 75 mg/kg/day based on increased incidences of clinical signs (scant feces and orange urine), mortalities, decreased food consumption, early delivery, abortion, and decreased body weight gain. Developmental NOAEL = 25 mg/kg/day Developmental LOAEL = 75 mg/kg/day based on premature deliveries, decreased gravid uterine weights, an increased litter incidence of a missing lobe of the lung, and decreased litter average for ossified sternal centra per fetus.
870.3800	Reproduction and fertility effects - rat	Parental/Systemic NOAEL = 31.2/36.8 mg/kg/day (M/F) Parental/Systemic LOAEL = 163.4/188.8 mg/kg/day (M/F) based on decreased body weight, body weight gain, and absolute and relative thymus weights. Reproductive NOAEL = 31.2/188.8 mg/kg/day (M/F) Reproductive LOAEL = 163.4/not established mg/kg/day (M/F) based on decreased sperm motility and increased number of sperm with detached heads in both generations. Offspring NOAEL = 9.8/11.5 mg/kg/day (M/F) Offspring LOAEL = 31.2/36.8 mg/kg/day (M/F) based on decreased body weight gains and delayed sexual maturation (M), decreased absolute thymus weights in F1 pups of both sexes, and an increase in stillbirths in both generations.
870.4100a	Chronic toxicity -rodents	See 870.4300, which includes requirements for both 870.4100 and 870.4200.

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Table A.2.2 Subchronic, Chronic and Other Toxicity Profile		
Guideline No.	Study Type	Results
870.4100b	Chronic toxicity - dog	NOAEL = 46.4/40.1 mg/kg/day (M/F) LOAEL = not established/52.9 mg/kg/day (M/F) based on clinical evidence of anemia in females. Note: dose-related decreases in ALT activity observed in mid- and high-dose males and females.
870.4200	Carcinogenicity -mouse	NOAEL = 171.4/65.1 mg/kg/day (M/F) LOAEL = 254.1/215.9 mg/kg/day (M/F) based on decreased body weight and body weight gain; decreased food consumption and food efficiency in males at the LOAEL. No evidence of carcinogenicity.
870.4300	Combined chronic feeding/ carcinogenicity - rat	NOAEL = 82.0/32.5 mg/kg/day (M/F) LOAEL = 156.5/97.8 mg/kg/day (M/F) based on decreased body weight and food consumption and altered hepatocellular eosinophilic focus of the liver in both sexes; ovary interstitial gland hyperplasia and increased lymphohistiocytic infiltrate in females; and slightly increased incidences of pelvic mineralization and transitional cell hyperplasia in the kidney, mottled livers of males. No evidence of carcinogenicity.
870.5100	Gene Mutation bacterial reverse mutation assay Parent	Small, but significant increase in frequency of histidine revertants in TA1535 strain treated at 1500 and 5000 ug/plate +/-S9; still present but weaker in its absence. The positive response was only reproducible at 5000 ug/plate +/-S9. Clothianidin considered mutagenic under conditions of this test.
870.5100	Gene Mutation bacterial reverse mutation assay Parent	No mutagenic activity in bacteria (<i>Salmonella typhimurium</i> and <i>Escherichia coli</i>) under conditions of this assay.
870.5100	Gene Mutation bacterial reverse mutation assay Parent	No mutagenic activity in bacteria (<i>Salmonella typhimurium</i>) under conditions of this assay.
870.5100	Gene Mutation bacterial reverse mutation assay Parent	Only TA 1535 tested. No mutagenic activity in bacteria (<i>Salmonella typhimurium</i>) under conditions of this assay.
870.5100	Gene Mutation bacterial reverse mutation assay BN0335E2 metabolite	No mutagenic activity in bacteria (<i>Salmonella typhimurium</i>) under conditions of this assay.
870.5100	Gene Mutation bacterial reverse mutation assay TZMU metabolite	No mutagenic activity in bacteria (<i>Salmonella typhimurium</i>) under conditions of this assay.
870.5100	Gene Mutation bacterial reverse mutation assay methyl guanidine intermediate	No mutagenic activity in bacteria (<i>Salmonella typhimurium</i>) under conditions of this assay.

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Table A.2.2 Subchronic, Chronic and Other Toxicity Profile		
Guideline No.	Study Type	Results
870.5100	Gene Mutation bacterial reverse mutation assay TZNG metabolite	No mutagenic activity in bacteria (<i>Salmonella typhimurium</i>) under conditions of this assay.
870.5100	Gene Mutation bacterial reverse mutation assay TMG metabolite	No mutagenic activity in bacteria (<i>Salmonella typhimurium</i>) under conditions of this assay.
870.5100	Gene Mutation bacterial reverse mutation assay BN0230M metabolite	No mutagenic activity in bacteria (<i>Salmonella typhimurium</i>) under conditions of this assay.
870.5100	Gene Mutation bacterial reverse mutation assay MAI metabolite	No mutagenic activity in bacteria (<i>Salmonella typhimurium</i>) under conditions of this assay.
870.5100	Gene Mutation bacterial reverse mutation assay N-Methylnitroguanidin intermediate	No mutagenic activity in bacteria (<i>Salmonella typhimurium</i>) under conditions of this assay.
870.5100	Gene Mutation - bacterial reverse mutation assay TI 435-Triazan intermediate	No mutagenic activity in bacteria (<i>Salmonella typhimurium</i>) under conditions of this assay.
870.5100	Gene Mutation - bacterial reverse mutation assay TI 435-CCMT-Adduct	No mutagenic activity in bacteria (<i>Salmonella typhimurium</i>) under conditions of this assay.
870.5300	Gene Mutation - <i>in vitro</i> mammalian cell gene mutation test (LS178Y TK +/- mouse lymphoma cells) Parent	Increases in mutant frequency with and without S9 at dose levels that were cytotoxic. The observed response was primarily due to small colony formation, indicating clastogenic activity.
870.5300	Gene Mutation - <i>in vitro</i> mammalian cell gene mutation test (V79-HPRT Assay) Parent	No increase in mutant frequency under the conditions of the study.
870.5395	Cytogenetics - mammalian erythrocyte micronucleus test Parent	Clothianidin is considered to be neither clastogenic nor aneugenic under these test conditions.
870.5375	Cytogenetics - <i>in vitro</i> mammalian chromosome aberration test (CHL Cells) Parent	Significant increases in frequency of cells with structural aberrations. Predominant types were chromatid breaks and exchanges. There was, however, no clear indication of a dose-related response in either the presence or absence of S9 activation.

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Table A.2.2 Subchronic, Chronic and Other Toxicity Profile		
Guideline No.	Study Type	Results
870.5500	Other Effects - DNA Repair Test in <i>Bacillus subtilis</i> Parent	No potential for DNA damage under these conditions.
870.5550	Other Effects - (UDS) in Mammalian Cells in Culture Parent	No evidence (or a dose related positive response) that UDS was induced.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile		
Guideline No.	Study Type	Results
870.6200a	Acute neurotoxicity screening battery - rat	NOAEL = Not established LOAEL = 100 mg/kg/day based on FOB findings (decreased arousal, motor activity, and locomotor activity).
870.6200b	Subchronic neurotoxicity screening battery - rat	NOAEL = 60.0/71.0 mg/kg/day (M/F) LOAEL = 177.0/200.1 mg/kg/day (M/F) based on slightly decreased food consumption, body weights, and body weight gains.
870.6300	Developmental neurotoxicity - rat	Maternal NOAEL = 42.9 mg/kg/day Maternal LOAEL = 142 mg/kg/day based on decreased body weights, body weight gains, and food consumption. Offspring NOAEL = 12.9 mg/kg/day Offspring LOAEL = 42.9 mg/kg/day based on decreased body weights, body weight gains, motor activity, and acoustic startle response in females.
870.7485	Metabolism and pharmacokinetics - rat	<p>Overall recovery: 95-100%. Readily absorbed and excreted within 96 hours following a single 2.5 mg/kg bw or repeated oral dose of 25 mg/kg bw, but at a dose of 250 mg/kg, absorption became biphasic and was saturated. Following single or multiple oral low doses (2.5 and 25mg/kg bw, respectively) of clothianidin, urinary excretion accounted for 89.2-94.6% of the administered radioactivity suggesting that a multiple exposure regimen did not affect the absorption/excretion processes. Urinary excretion unaffected following single 250 mg/kg dose. Excretion via the feces accounted for the remainder of the administered radioactivity in all treatment groups (3.8-8.6%). Rapid absorption and distribution of administered radioactivity to all organs and tissues followed by rapid excretion with reduction to background levels in most tissues and organs within 24 hours. Somewhat greater rate of absorption and elimination in females. Excretory patterns did not exhibit gender-related variability but reflected the delayed absorption in the high-dose group. Neither clothianidin nor metabolites appear to undergo significant sequestration.</p> <p>The metabolites identified (primarily oxidative demethylation products and cleavage products of the nitrogen-carbon bond between the nitroimino and thiazolyl moieties) were consistent with Phase I processes. Extraction efficiencies appeared to be excellent and most components in all of the matrices examined (urine, feces, and tissues) were adequately quantified and characterized. The available data, based upon studies using both the nitroimino- and the thiazolyl-2-labeled clothianidin, affirmed the metabolism pathway proposed by the investigators.</p>

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile		
Guideline No.	Study Type	Results
870.7485	Metabolism and pharmacokinetics - mouse	<p>Of the administered radioactivity, 98.7-99.2% was recovered. Readily absorbed and excreted within 168 hours following a single oral dose of 5 mg/kg body weight. Urine was the major route of excretion, accounting for 92.4-93.7% of the administered radioactivity. Feces accounted for 5.0-6.8% of the administered radioactivity. Within 24 hours, 89.0-91.7 % of the administered radioactivity was excreted in the urine and 4.9-6.2% was excreted in the feces. Residual radioactivity in any given tissue at 168 hours post-dose was considerably less than 1% of the administered dose. Therefore, neither clothianidin nor its metabolites appeared to exhibit potential for bioaccumulation. Excretory patterns did not exhibit gender-related variability.</p> <p>Both urinary and fecal metabolites were identified using TLC and radioautography in conjunction with known standards and were quantified by TLC/LSC . The major metabolites in both urine and feces were the parent compound (clothianidin) and TZNG [N-(2-chlorothiazol-5-ylmethyl)-N\square-nitroguanidine] which resulted from N-demethylation of clothianidin. Extraction efficiencies were excellent and most components in the urine and feces were adequately quantified and characterized. Based on the data from the oral administration of [nitroimino-14C]-clothianidin the metabolism pathway proposed by the investigator's was supported.</p>
870.7600	Dermal penetration - monkey	<p>Dermal absorption as the sum of urinary and fecal excretion and Cage/Pan/Cbair Wash, Debris was 0.24 (+ 0.11) as percent of dose. Adjustment of the direct absorption determination was not necessary because recovery from the dermal dose was >90%.</p> <p>A value of 1% dermal absorption was considered appropriate for use in risk assessment. This estimation takes into account any variability that would have likely occurred with testing several dose levels.</p>
870.7800	Immunotoxicity – rat (adults)	<p>Immunotoxicity NOAEL = 253 mg/kg/day (M/F)</p> <p>Immunotoxicity LOAEL = not established</p> <p>At the highest dose tested, 253 mg/kg/day, a decrease in body weights, body weight gains, and food consumption was noted in adult males and females.</p>
Non-guideline	Special Study: Neurotoxicity and pharmacology - mouse	<p>NOAEL = 25 mg/kg/day (M/F)</p> <p>LOAEL = 50 mg/kg/day (M/F) based on transient signs of decreased spontaneous motor activity, tremors, and deep respirations.</p>



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: 10/23/2007

MEMORANDUM

SUBJECT: Cyfluthrin/Beta-cyfluthrin – Human Health Risk Assessment For New Uses on Grasses, Alfalfa, and Sugar Beet Seed and Revised Tolerances on Cereal Grain Commodities.

Regulatory Action: Section 3 Registration Action

Risk Assessment Type: Single Chemical Aggregate

PC Codes: 128831 – Cyfluthrin

118831 – Beta-cyfluthrin

Petitions 6E7058, 6F7160, 7F7226, and 7F7200.

DP Barcode: D331951; D331952; D335486; D339095; D339413; D339414;
D339415; D339445; D340710; D340711; D340712; D340713.

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TO: Marion Johnson, Chief
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And

Dan Rosenblatt, Chief
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Summary: HED has completed a human health risk assessment for the proposed uses of and tolerances for cyfluthrin/beta-cyfluthrin associated with the subject petitions: 6E7058 – use on grasses; 6F7160 – new use on sugar beet seed; 7F7200 – crop group tolerances; and, 7F7226 – increased application rate on alfalfa. The dietary assessment reflects proposed new uses and tolerances, and includes an updated drinking water assessment. While there are no residential exposures associated with the subject petitions, an aggregate assessment was conducted based on currently registered residential uses. An occupational exposure assessment has also been performed for the proposed uses on grasses, alfalfa, and sugar beet seed treatment.

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1.0 Executive Summary

Cyfluthrin and beta-cyfluthrin (an enriched isomer of cyfluthrin) are non-systemic pyrethroid insecticides. Cyfluthrin was first registered in 1989, and currently there are approximately 145 active products registered for use on a wide variety of sites including agricultural, indoor/outdoor domestic dwellings, ant dens/mounds, and stored product pests. Beta-cyfluthrin was first registered in 1995 and currently there are approximately 27 active registrations. Permanent tolerances are established for residues of cyfluthrin (40 CFR §180.436). Tolerances for cyfluthrin also cover beta-cyfluthrin, provided that the use rates for beta-cyfluthrin are $\frac{1}{2}$ that of cyfluthrin. The current risk analysis on cyfluthrin/beta-cyfluthrin was conducted to assess several petitions; (i) an increase in the number of applications to alfalfa; (ii) expanded geographical uses on grasses; (iii) request for crop group 15 (except rice) and for crop group 16 tolerances; and, (iv) a new use for sugar beet seed treatment. A summary of the subject petitions can be found in Table 1. Several field trial studies were submitted in connection with the subject petitions which were reviewed and incorporated into this assessment.

Toxicologically, the primary target for cyfluthrin/beta-cyfluthrin is the neuromuscular system; other non-specific effects include decreased body weight gain, and decreased food consumption. The observed neuromuscular effects (tremors, gait abnormalities, abnormal postural reactions, splaying of limbs and decreases in activity) occurred mainly in oral studies in the dog and the rat. In general, the toxicity data base does not indicate that any major differences in toxicity exist between beta-cyfluthrin and cyfluthrin via the oral route. Data from the inhalation toxicity study showed evidence of clinical signs as well as hypothermia and decreased body weight gains. In a postnatal inhalation study in mice, there were clinical signs of neurotoxicity in the pups as well as increased spontaneous motor activity and paresthesia (tingling, burning or prickling – also seen in oral studies).

In oral developmental studies no increased susceptibility was observed in the rat or rabbit; however, increased susceptibility was observed in inhalation developmental studies. Increased susceptibility was also seen in oral reproduction studies and in a developmental neurotoxicity study on beta-cyfluthrin. The data also demonstrate increased susceptibility of rats and mice to cyfluthrin postnatally. The FQPA Safety Factor was reduced to 1x because the database is complete and the exposure database is sufficient.

The database does not indicate that either cyfluthrin or beta-cyfluthrin induces any endocrine disruption; and, there is no concern of mutagenicity. HED has classified cyfluthrin/beta-cyfluthrin as “not likely to be carcinogenic to humans.”

The metabolism of cyfluthrin/beta-cyfluthrin is well understood in both plant and animal matrices, and analytical methods for the currently registered and proposed uses have been submitted and validated.

The dietary analysis is refined and includes processing factors, percent crop treated estimates, and monitoring data. The dietary analysis also includes secondary residues, and reflects revised tolerance values associated with the subject petitions. The updated drinking water analysis considers all currently registered and proposed uses.

Acute dietary risks for the general population and all population subgroups were not of concern to HED, with children 1 – 2 years old, the highest exposed subpopulation, utilizing 53% of the acute population adjusted dose (aPAD). Chronic dietary risks for the general population and all population subgroups were also not of concern to HED, with children 1 – 2 years old, the highest exposed subpopulation, utilizing 17% of the chronic population adjusted dose (cPAD).

Aggregate assessments were also conducted for cyfluthrin/beta-cyfluthrin. The acute aggregate assessment included food and drinking water only, and therefore is equal to the acute dietary risk (children 1 – 2 years utilizing 53% of the aPAD). In the short-, and intermediate-term assessments, HED combined the current chronic dietary exposure estimates with (previously assessed) residential exposures. (The current petitions do not indicate any potential residential or non-occupational exposures). Aggregate assessments indicated no risks of concern.

HED's occupational risk assessment examined risk to workers associated with production of alfalfa, production of grasses, and for seed treatment operations. HED's analysis indicates that handlers using aerial or ground boom equipment for alfalfa or grass production are required to wear base line protective equipment (PPE), chemical resistant gloves, and a dust/mist respirator when handling liquid formulations of cyfluthrin/beta-cyfluthrin; but, are adequately protected with just base line PPE when handling water soluble bag packaged wettable powder formulations. Applicators and flaggers involved in alfalfa and grass production were also adequately protected with base line PPE. Exposure to workers entering cyfluthrin and beta-cyfluthrin treated fields to perform post-application activities is not of concern.

Risks to individuals associated with sugar beet seed treatment were also assessed. Risks of concern existed for certain scenarios. Intermediate-term exposure to loaders/treaters involved in sugar beet seed treatment was a concern to HED (MOE = 81). Also, risks to an individual performing all three seed treatment operations, (i.e., performing loading/treating, bagging, and sewing in one 8-hour work day) was of concern to HED. Risks to other individuals involved in the seed treatment operation were not of concern to HED. Also, risks to workers who plant the Poncho Beta treated sugar beet seed are not a concern to HED.

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies, which comprise the Pesticide Handlers Exposure Database (PHED), have been determined to require a review of their ethical conduct, and have received that review. The studies in PHED were considered appropriate (or ethically conducted) for use in risk assessments.

Potential areas of environmental justice concerns, to the extent possible, were considered for this human health risk assessment, in accordance with US Executive Order 12898, Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations, <http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf>.

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that

subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by USDA under the CSFII, and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Whenever appropriate, non-dietary exposures based on home use of pesticide products, associated risks for adult applicators, and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

A separate but related petition (6F7159) was also submitted regarding the proposed (Poncho Beta®) use on sugar beet seed. The active ingredient being addressed in Petition 6F7159 is clothianidin, which is a co-active ingredient along with beta-cyfluthrin in Poncho Beta®. The occupational risks associated with clothianidin are addressed in a separate document (D340131). Together these two documents address the occupational risks associated with the proposed use of Poncho Beta® for sugar beet seed treatment.

Summary of Recommendations

- HED recommends directions for use of Baythroid® 2, Renounce® 20WP, and Baythroid® XL, be amended to exclude ultra-low volume applications to grasses and alfalfa.
- HED recommends the Addition of dust/mist respirators as a PPE requirement for all liquid formulations of Baythroid® 2, Renounce® 20WP, and Baythroid® XL.
- HED recommends the Registration Division consider the occupational risks associated with the proposed use of Poncho Beta® in light of the exposures from both beta-cyfluthrin and clothianidin prior to granting this sugar beet seed treatment use and its associated tolerances.
- Pending amendments and changes suggested to the proposed Baythroid® 2, Renounce® 20WP, and Baythroid® XL labels, HED recommends the registration of new uses and establishment of tolerances for cyfluthrin/beta-cyfluthrin.
- HED recommends that the establishment of tolerances incorporates the correct commodity definitions for cyfluthrin (and beta-cyfluthrin) treated commodities as stated in Appendix C, Table 1 and in the table below in this section.
- A revised Section F is required reflecting HED recommendations, and for the establishment of (separate) tolerances listed below for both cyfluthrin and beta-cyfluthrin. The cyfluthrin tolerances should be included in 40CFR§180.436(a)(1), while a separate section under 180.436 should be established for tolerances for beta-cyfluthrin, analogous to the tolerances for lambda-cyhalothrin and gamma-cyhalothrin in §180.438. The section for beta-cyfluthrin needs to be established because registrations for cyfluthrin on

these commodities might be cancelled at some point in the future. The tolerances for cyfluthrin and beta-cyfluthrin should be established at the same levels. The recommended wording for the beta-cyfluthrin tolerance expression is as follows:

"Tolerances are established for residues of the insecticide beta-cyfluthrin [mixture comprising the enantiomeric pair (R)- α -cyano-4-fluoro-3-phenoxybenzyl (1S,3S)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate and (S)- α -cyano-4-fluoro-3-phenoxybenzyl (1R,3R)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate with the enantiomeric pair (R)- α -cyano-4-fluoro-3-phenoxybenzyl (1S,3R)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate and (S)- α -cyano-4-fluoro-3-phenoxybenzyl (1R,3S)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate] in or on the following commodities:"

- HED also recommends that, at some point in the future, tolerances be established for all food uses of beta-cyfluthrin (i.e., on those commodities not included in the present actions) under the new section to be created under 40 CFR §180.436.

Commodity	Recommended Tolerance (ppm)
Grass, forage, fodder and hay, group 17, forage	12
Grass, forage, fodder and hay, group 17, hay	50
Alfalfa, forage	5.0
Alfalfa, hay	13
Beet, sugar, roots	0.10
Beet, sugar, dried pulp	1.0
Barley, grain	0.15
Buckwheat, grain	0.15
Millet, grain	0.15
Oat, grain	0.15
Rye, grain	0.15
Wheat, grain	0.15
Corn, field, grain	0.05
Corn, sweet, kernel plus cob with husks removed	0.05
Sorghum, grain, grain	3.5
Wheat, bran	0.5
Corn, field, refined oil	None*
Rice, bran	None
Rice, hulls	None
Grain, cereal, forage, fodder and hay, group 17, forage, except rice	25
Grain, cereal, forage, fodder and hay, group 17, stover, except rice	30
Grain, cereal, forage, fodder and hay, group 17, straw, except rice	7.0
Grain, cereal, forage, fodder and hay, group 17, hay except rice	6.0
Wheat, forage	None
Corn, field, forage	None
Corn, sweet, forage	None
Sorghum, grain, forage	None
Corn, field, stover	None
Corn, pop, stover	None
Corn, sweet, stover	None
Sorghum, grain, stover	None
Wheat, hay	None

Commodity	Recommended Tolerance (ppm)
Wheat, straw	None
Cattle, fat	2.0
Cattle, meat	0.10
Cattle, meat byproducts	0.10
Goat, fat	2.0
Goat, meat	0.05
Goat, meat byproducts	0.05
Hog, fat	0.5
Hog, meat	0.01
Hog, meat byproducts	0.01
Horse, fat	2.0
Horse, meat	0.05
Horse, meat byproducts	0.05
Milk	0.2
Milk, fat	5.0
Sheep, fat	2.0
Sheep, meat	0.05
Sheep, meat byproducts	0.05

*"None" indicates that an existing tolerance on that commodity should be revoked.

Table 1. Summary of Regulatory Actions for Current Cyfluthrin/Beta-cyfluthrin									
Petition/ DP Barcode	Petition Request	Label Trade Name/ EPA Reg. Number/ Active Ingredient	Product Formulation	Label Information			Assessment Conducted (Document Barcode Ref.)		
				Current Label Rates		Proposed Label Rates	No. of App.		No. of App
				Max Single Rate	No. of App.		Max Single Rate		
6E7058	Request for use on grasses throughout the U.S. (pasture/rangeland/grass for seed/grass for hay/grass in mixed stands with alfalfa)	Baythroid® 2 (264-745) <i>cyfluthrin</i>	EC	0.044	3	0.044		4	Residue chemistry (D 339413)
D339445		Renounce® 20WP 264-784 <i>cyfluthrin</i>	WP/WSP	Not on label	Not on label	0.044		4	Dietary (D339414)
D331952		Baythroid® XL 264-840 <i>beta-cyfluthrin</i>	EC	0.022	3	0.022		4	Occupational (D339445)
D331951									
6F7160	Request for new use on sugar beet seed	Poncho Beta (264-RNLA) 264-RNLA <i>beta-cyfluthrin</i> (clothianidin)	Liquid	No existing use, new use is being proposed.		5.07 fl. oz/unit seed (100,000 seeds)		1	Residue chemistry (D 339413)
D335486									Dietary (D339414)
D339413									Occupational (D339445)
D339414									
D339415									
7F7200	Request to amend labels to include Crop Group 15 (except rice) and Crop Group 16; Establish tolerance for Crop Group 15 (except rice) and Crop Group 16	Baythroid® XL 264-840 <i>beta-cyfluthrin</i>	EC	0.019 – 0.022	2 - 10	No proposed change to this label in connection to this petition.			Residue chemistry (D 339413)
D339095									Dietary (D339414)
									Occupational (D339445)
7F7226	Increased seasonal rate on alfalfa (increased no. of applications); Increased tolerance on alfalfa	Baythroid® 2 264-745; <i>cyfluthrin</i>	EC	0.044	~5	0.044		8	Residue chemistry (D 339413)
D340710		Renounce® 20WP 264-784 <i>cyfluthrin</i>	WP/WSP	0.044	~5	0.044		8	Dietary (D339414)
D340711		Baythroid® XL 264-840 <i>beta-cyfluthrin</i>	EC	0.022	4	0.022		8	Occupational (D339445)
D340712									
D340713									

Baythroid® 2 (264-745) contains cyfluthrin at 25%; Renounce® 20WP (264-840) contains cyfluthrin at 20%
Baythroid® XL (264-840) contains beta-cyfluthrin at 12.7%; Poncho Beta® contains beta-cyfluthrin at 4.6% and clothianidin at 34.3%.

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2.0 Ingredient Profile

Both cyfluthrin and beta-cyfluthrin are mixtures of the same four diastereomers. Isomers I and II are in the *cis* configuration, and Isomers III and IV are in the *trans* configuration. Cyfluthrin is comprised of approximately equal parts: Isomer I is approximately 25%, Isomer II is approximately 19%, Isomer III is approximately 34% and, Isomer IV is approximately 23%. Beta-cyfluthrin on the other hand, is enriched in Isomer II (approximately 35%) and Isomer IV (approximately 62%), and contains only minor amounts of Isomer I and Isomer III (less than 3% of total). The nomenclature and physicochemical properties of cyfluthrin and beta-cyfluthrin are presented below in Tables 2 and 3.

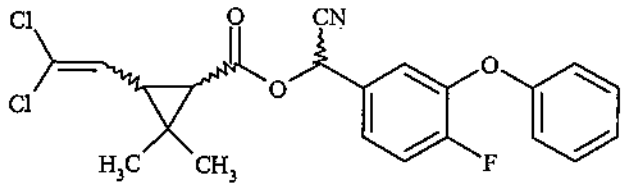
Table 2. Cyfluthrin and β -Cyfluthrin Nomenclature.	
	 <p>Diastereomer I (1R,3R,αR + 1S,3S,αS; 1:1; <i>cis</i>) Diastereomer II (1R,3R,αS + 1S,3S,αR; 1:1; <i>cis</i>) Diastereomer III (1R,3S,αR + 1S,3R,αS; 1:1; <i>trans</i>) Diastereomer IV (1R,3S,αS + 1S,3R,αR; 1:1; <i>trans</i>)</p> <p>Cyfluthrin: Isomer I (23-27%), Isomer II (17-21%), Isomer III (32-36%), and Isomer IV (21-25%) beta-Cyfluthrin: Isomer I (<2%), Isomer II (30-40%), Isomer III (<3%), and Isomer IV (57-60%)</p>
Common names	Cyfluthrin and beta-Cyfluthrin
Company experimental name	Baythroid®, FCR1272
IUPAC names	<p>Cyfluthrin: (RS)-α-cyano-4-fluoro-3-phenoxybenzyl (1RS,3RS;1RS,3SR)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate</p> <p>beta-Cyfluthrin: enantiomeric pair (R)-α-cyano-4-fluoro-3-phenoxybenzyl (1S,3S)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate and (S)-α-cyano-4-fluoro-3-phenoxybenzyl (1R,3R)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate in ratio 1:2 with the enantiomeric pair (R)-α-cyano-4-fluoro-3-phenoxybenzyl (1S,3R)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate and (S)-α-cyano-4-fluoro-3-phenoxybenzyl (1R,3S)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate</p>
CAS name	cyano(4-fluoro-3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate
CAS registry number	68359-37-5
End-use products (EPs)	<p>Cyfluthrin: Baythroid® 2 (2 lb/gal EC; EPA Reg. No. 264-745) Renounce® 20WP (20% WP; EPA Reg. No. 264-784)</p> <p>beta-Cyfluthrin: Baythroid® XL (1 lb/gal EC; EPA Reg. No. 264-840)</p>

Table 3. Physicochemical Properties of Technical Grade Cyfluthrin	
Parameter	Value
Melting point/range (°C)	Isomer I: 57 Isomer II: 73-74 Isomer III: 65-66 Isomer IV: 101-102
pH	not measurable because of low solubility in water
Density (g/mL at 20°C)	1.28
Water solubility (µg/L at 20°C)	Isomer I: 2.2 Isomer II: 1.9 Isomer III: 2.2 Isomer IV: 2.9
Solvent solubility (g/L room temperature)	Methylene chloride >200 Toluene >200 Hexane 10-20 Isopropanol 20-50
Vapor pressure (20 or 25°C)	7.2×10^{-9} Pa
Dissociation constant, pK_a	does not dissociate
Octanol/water partition coefficient, $\text{Log}(K_{ow})$	Isomer I: 6 Isomer II: 5.9 Isomer III: 6 Isomer IV: 5.9
UV/visible absorption spectrum	Absorption maxima: primary: 196 nm, secondary 275 nm

3.0 Hazard Characterization/Assessment

3.1 Database Summary

3.1.1 Studies Available and Considered

Available mammalian toxicology studies considered in the hazard characterization include:

- Cyfluthrin
 - acute oral, dermal, and inhalation toxicity; eye and dermal irritation; and dermal sensitization studies
 - subchronic oral, dermal, and inhalation toxicity studies in rats
 - prenatal developmental oral toxicity studies in rats and rabbits
 - prenatal developmental inhalation toxicity studies in rats
 - special postnatal inhalation study in mice
 - multi-generation reproduction studies in rats
 - chronic/carcinogenicity studies in rats and mice; chronic study in dogs
 - a complete battery of mutagenicity studies
 - delayed neurotoxicity oral and dermal studies in hens
 - metabolism studies in rats
- Beta-cyfluthrin
 - acute oral, dermal, and inhalation toxicity; eye and dermal irritation; and dermal sensitization studies
 - subchronic oral toxicity studies in rats and dogs
 - subchronic inhalation toxicity study in rats
 - prenatal developmental oral toxicity study in rats
 - a complete battery of mutagenicity studies
 - acute, subchronic, and developmental neurotoxicity studies in rats

3.1.2 Mode of Action, Metabolism, Toxicokinetic Data

Mode of Action

Cyfluthrin is a type II pyrethroid (i.e., it has a cyano group at the α carbon position of the alcohol moiety, and it is more effective when the ambient temperature is raised); beta-cyfluthrin is an enriched isomer of cyfluthrin. Pyrethroids initially stimulate nerve cells to produce repetitive discharges which can eventually lead to paralysis. Such effects are caused by their action on the sodium channel through which sodium ions enter the axon to cause excitation. These effects are produced in an insect's nerve cord, which contains ganglia and synapses, as well as in giant nerve fiber axons.¹ Type II pyrethroids give rise to the C-S syndrome of clinical signs of toxicity. The C-S syndrome consists of initial pawing and burrowing and later abnormal movements, salivation, coarse tremors, and convulsions.

Toxicokinetic Data

Following oral administration, cyfluthrin is rapidly and nearly completely absorbed. In radiolabeled studies, peak plasma levels occurred at about 2 hours after dosing. Greater than 95% of the administered radioactivity was excreted within 48 hours. Radioactivity was excreted in the urine and feces with virtually none being excreted in expired air. The ratio of radioactivity in urine/feces was higher in males than in females. About 50% of the total urinary radioactivity was recovered during the first 6-8 hours after dosing and about 90% within the first 24 hours. At 48 hours, only the fat tissue (renal fat) contained levels of radioactivity that clearly exceeded the overall mean body level, being 6-11X higher. Different dose levels (0.5 or 10 mg/kg) or pretreatment (14X) did not appreciably affect the above findings. Results following intravenous dosing were quite similar to those described for oral dosing. Studies in male rats with bile fistulas indicated an enterohepatic circulation of test material. Parent cyfluthrin is cleaved at the ester bond and then oxidized to yield 3-phenoxy-4-fluorobenzoic acid. This intermediate is then either hydroxylated and subsequently conjugated and excreted, or first bound to glycine and then hydroxylated, conjugated and excreted.

A comparative study in rats on the absorption of cyfluthrin after a single dose indicates that when cremophor EL is used as the vehicle, the concentration of cyfluthrin in the blood peaks after 1 hour and the rats show signs of intoxication; whereas, when PEG 400 is used as the vehicle, the blood level peaks at 6 hours after dosing and the maximum blood level is about 1/5 of the level when the test substance is administered with cremophor. There was more cyfluthrin in the stomachs of the rats treated with PEG 400 than there was in the stomachs of those treated with cremophor. Cyfluthrin appears to be absorbed more quickly from the GI tract in the presence of cremophor than in the presence of PEG 400.

¹ Ware, G.W. *The Pesticide Book*. Fresno, CA, Thomson Publications, 1994, pgs 171-172.

3.1.3 Sufficiency of Studies/Data

Cyfluthrin toxicity data have been used as bridging data for beta-cyfluthrin. The toxicology databases together are considered complete and adequate for selecting toxicity endpoints for risk assessment. The scientific quality is relatively high, and the toxicity profiles of both cyfluthrin and beta-cyfluthrin can be characterized for all effects, including potential developmental, reproductive, and neurotoxic effects.

3.2 Toxicological Effects

The HED risk assessment team has re-evaluated the cyfluthrin/beta-cyfluthrin toxicological effects and endpoints for assessing human health risk. For a complete discussion of the toxicological effects of cyfluthrin and beta-cyfluthrin, excluding the recently received developmental neurotoxicity study, refer to "Toxicology Chapter for Cyfluthrin/Beta-Cyfluthrin" (D283924, V. Dobozy, 7/18/2002).

The acute toxicity of both cyfluthrin and beta-cyfluthrin is low to high via the oral route of exposure (Categories I to III, depending on the vehicle), moderate via the inhalation route (Categories II to III, depending upon the vehicle), and low via the dermal route (Category IV). Cyfluthrin and beta-cyfluthrin are slight eye and dermal irritants, but neither is a dermal sensitizer.

The databases on cyfluthrin and beta-cyfluthrin indicate one major target for these chemicals, the neuromuscular system, along with non-specific effects such as decreased body weight gain and food consumption. The neuromuscular effects (i.e., tremors, gait abnormalities, abnormal postural reactions, splaying of limbs, and decreases in activity) occurred mainly in oral studies in the dog and the rat. In some studies in rats and mice, ear lesions were observed, which appear to be related to a known pyrethroid effect, paresthesia (tingling, burning or prickling), which caused the animals to scratch excessively.

In oral studies with the rat, beta-cyfluthrin appeared more toxic than cyfluthrin; however, in the oral studies with the dog (the most sensitive species for clinical signs), beta-cyfluthrin did not appear to be more toxic than cyfluthrin. Weight of the evidence from the cyfluthrin rat studies (28-day feeding and gavage studies, subchronic feeding study, 14-day and 5-month neurotoxicity studies (gavage), chronic feeding studies and the reproduction studies) indicates that the clinical signs of neurotoxicity in the rat may commence at a dose level somewhere between 40 and 60 mg/kg/day. In the 90-day oral study with beta-cyfluthrin, clinical signs of neurotoxicity were observed at 37.0/43.0 mg/kg/day (M/F), and in the 90-day subchronic neurotoxicity study with beta-cyfluthrin, clinical signs of neurotoxicity were observed at 27/30 mg/kg/day (M/F). Comparison of the developmental rat studies indicates that the LOAEL for beta-cyfluthrin is 10 mg/kg/day (decrease in body weights and food consumption); whereas, the LOAEL for cyfluthrin is greater than 10 mg/kg/day (although some slight effects were observed in the range-finding study at this dose level). In contrast to the rat, when all of the available dog studies are considered, gait abnormalities were observed at 13.9 mg/kg/day in the 90-day dog study with beta-cyfluthrin (NOAEL = 2.36 mg/kg/day), while the LOAELs from three dog feeding studies

on cyfluthrin (i.e., one 6-month and two 12-month studies) were based on similar effects and occurred at similar doses of 15, 16, and 10.6 mg/kg/day (NOAELs = 5, 4, and 2.4 mg/kg/day). A comparison of these NOAELs does not indicate any major differences in toxicity between beta-cyfluthrin and cyfluthrin in the oral studies. The studies also do not indicate any increase in the severity of the effects over time (the NOAEL and LOAEL from the new dog study is lower because of dose spread). In addition, the NOAELs for the 28-day dog study and the 90-day dog study conducted with beta-cyfluthrin are similar. Therefore, it is unlikely that a NOAEL from a chronic dog study conducted with beta-cyfluthrin would be less than the NOAEL for the 90-day study conducted with beta-cyfluthrin. In the dog, the neurological clinical signs induced by pyrethroids in general do not appear to be cumulative but rather, are transient. In general, neither sex appears to be more sensitive, for either dogs or rats.

The inhalation studies in the rat, cyfluthrin induced some clinical signs, but these were not as severe as in the oral studies (e.g., reduced motility, dyspnea, piloerection, ungroomed coat, and eye irritation). In addition to the clinical signs, hypothermia and decreased body weight gains were also observed in the rat inhalation studies. In a postnatal inhalation study in mice, there were clinical signs of neurotoxicity in the pups as well as increased spontaneous motor activity and paresthesia. The inhalation toxicity of beta-cyfluthrin and cyfluthrin can be compared through examination of the 4-week studies on each compound, both of which used a common vehicle. A direct comparison is somewhat limited by the differences in dose spacing; however, the studies show that the NOAELs and LOAELs are not significantly different: the NOAEL and LOAEL for the study conducted with cyfluthrin are 0.12 and 1.6 mg/kg/day, respectively and the NOAEL and LOAEL for the study conducted with beta-cyfluthrin are 0.07 and 0.73 mg/kg/day, respectively. Both LOAELs are based on similar effects, including body weight changes, with additional effects seen at the higher dose of 1.6 mg/kg/day in the cyfluthrin study.

A number of the non-acute gavage studies conducted with cyfluthrin and beta-cyfluthrin used cremophor as the vehicle. Therefore, the toxicity of the two isomer mixtures is probably enhanced in these studies. The repeated-dose dermal study conducted with cyfluthrin in the rat validates this finding. In that study, the only systemic effects observed were at the limit dose of 1077 mg/kg/day (decreased food consumption, red nasal discharge and urine staining). All of the longer term inhalation studies conducted with cyfluthrin and beta-cyfluthrin use a PEG vehicle and it is likely that the same enhancement holds true as well. These vehicles can cause damage to the lungs. The repeated dose dermal study (18 applications) indicates that, with repeated dermal exposure, significant dermal irritation will result. The NOAEL for skin irritation in that study is 113 mg/kg/day and the LOAEL is 376 mg/kg/day.

Multiple hen studies by the oral, dermal and inhalation routes of administration indicate that cyfluthrin is not a delayed neurotoxicant and does not inhibit neurotoxic esterase.

Cyfluthrin has been classified as a Category E carcinogen (no evidence of carcinogenicity) and, with the submission of new studies, is reclassified as "not likely to be carcinogenic to humans" under the Draft Proposed Guidelines for Carcinogen Risk Assessment (1999). No increase in any type of tumors was found in rats or mice in the available carcinogenicity studies, although structure-activity comparisons reveal indications of lung tumors in mice with three other pyrethroids. No evidence of mutagenicity was seen in any of the eight acceptable studies on

cyfluthrin or the five acceptable studies on beta-cyfluthrin. The submitted studies on cyfluthrin satisfy the pre-1991 mutagenicity test battery.

3.3 FQPA Considerations

The cyfluthrin/beta-cyfluthrin risk assessment team has considered the toxicity data regarding sensitivity of infants and children. For a more in-depth description of the FQPA considerations associated with cyfluthrin and beta-cyfluthrin, excluding the recently received developmental neurotoxicity study, refer to "CYFLUTHRIN and BETA-CYFLUTHRIN - 3rd Report of the Hazard Identification Assessment Review Committee." (TXR 0050768, P. Hurley, 5/21/2002).

The mammalian toxicology database for cyfluthrin and beta-cyfluthrin is complete and adequate for FQPA considerations. Studies available include prenatal developmental oral toxicity studies with rats (cyfluthrin and beta-cyfluthrin) and rabbits (cyfluthrin only); prenatal developmental inhalation toxicity studies (cyfluthrin) in rats; a special postnatal inhalation toxicity study (cyfluthrin) in mice; multi-generation reproduction studies (cyfluthrin) in rats; delayed neurotoxicity oral studies (cyfluthrin) in hens; and acute, subchronic, and developmental neurotoxicity (DNT) studies (beta-cyfluthrin) in rats.

Evidence of neurotoxicity typical of the pyrethroids was observed throughout the toxicology database. In the acute and subchronic neurotoxicity studies, clinical signs of neurotoxicity, changes in Functional Observational Battery (FOB) measurements, and decreased motor activity were seen. In the DNT study, decreased brain weights were seen in female offspring at study termination along with decreased body weights and body weight gains in pups of both sexes. In the other guideline studies on rats, dogs, and mice, neurotoxic effects including clinical signs of neurotoxicity, gait abnormalities, changes in motor activity, tremors, and abnormal postural reactions were seen following oral and inhalation exposure.

There is a concern for pre- and/or postnatal toxicity resulting from exposure to cyfluthrin and beta-cyfluthrin. In the prenatal developmental studies, there was no evidence of increased susceptibility of rats or rabbits to *in utero* exposure to either cyfluthrin or beta-cyfluthrin via the oral route; however, there was evidence of increased qualitative and quantitative susceptibility of rats to *in utero* exposure to cyfluthrin via the inhalation route. A postnatal inhalation study in mice demonstrates increased qualitative and quantitative susceptibility of the offspring following exposure to cyfluthrin. Increased susceptibility is also seen in rats in oral reproduction studies on cyfluthrin and in a developmental neurotoxicity study on beta-cyfluthrin.

The degree of concern for all of the prenatal developmental, special postnatal, reproduction, and developmental neurotoxicity studies that demonstrate increased susceptibility (quantitative and/or qualitative) is low because the effects in each of these studies are well characterized, with conservative NOAELs established for all developmental and offspring effects. There are no residual uncertainties because the points of departure (NOAELs) selected for risk assessment are lower than the NOAELs from these studies and are, thus, protective of any potential pre- and post-natal effects.

There are no residual uncertainties identified in the exposure databases. The acute dietary exposure assessment is refined, and drinking water estimates were derived from conservative screening models. Although refined, HED believes that the dietary assessment is based on reliable data and will not underestimate exposure/risk. The residential exposure assessment utilizes reasonable high-end variables set out in HED's Occupational/Residential Exposure SOPs. The aggregate assessment is based upon reasonable worst-case residential assumptions, and is also not likely to underestimate exposure/risk to any subpopulation, including those comprised of infants and children.

Based on the data discussed above, the FQPA Safety Factor can be removed (i.e., reduced to 1X) due to the completeness of the toxicology database, the lack of residual concerns regarding pre- and post-natal toxicity, and the reliance on exposure data that are unlikely to underestimate exposure to the pesticide.

3.4 Hazard Identification and Toxicity Endpoint Selection

3.4.1 Acute Reference Dose (aRfD) – General Population

Study Selected: Acute neurotoxicity study in rats (beta-cyfluthrin)

MRID Number: 44401101

Dose and Endpoint for Risk Assessment: 2 mg/kg (NOAEL), based on clinical signs, changes in FOB parameters, and decreases in motor activity observed at 10 mg/kg (LOAEL)

Uncertainty Factor(s): 100X (10X for interspecies variability, 10X for intraspecies variability)

Comments about Study/Endpoint/Uncertainty Factor:

This endpoint for the general population is based on effects observed after a single dose, which is the appropriate duration of exposure for an acute endpoint, and the route of administration (oral) is appropriate for dietary considerations. Selection of the acute dietary endpoint based on the acute neurotoxicity (ACN) study is considered protective, as the vehicle used in this study was cremophor, which has been shown to enhance absorption of cyfluthrin, by increasing the amount of cyfluthrin in the blood. However, the NOAEL of 2 mg/kg in the ACN study where cremophor was the vehicle is supported by a NOAEL of 2.36 mg/kg in the 90-day dog feeding study where beta-cyfluthrin was mixed directly into the feed (i.e., no vehicle was used). The LOAEL in this dog study was based on gait abnormalities seen following 3 days of exposure to 13.9 mg/kg/day, similar to the effects seen after a single dose of 10 mg/kg in the ACN study. Selection of an endpoint based on a beta-cyfluthrin study is considered protective of effects from both beta-cyfluthrin and cyfluthrin, as beta-cyfluthrin is an enriched isomer of cyfluthrin.

A separate endpoint for acute dietary exposure to females 13-49 was not selected because the acute reference dose for the general population is protective of any potential developmental effects. No developmental effects are observed in any of the developmental studies at dose levels in the 2 mg/kg range. In the rat developmental toxicity study with beta-cyfluthrin, increases in skeletal variations were observed at 40 mg/kg/day (NOAEL = 10 mg/kg/day); however, these effects generally consisted of changes in ossification rates likely to be connected with an observed decrease in mean fetal body weights, which are not considered to be single dose effects. Further, most of these differences were seen in the number of fetuses affected and

not in the number of litters affected. The acute reference dose for the general population is also protective of the offspring effects seen in the developmental neurotoxicity study with beta-cyfluthrin, which included decreased brain weights in females at study termination, at 17.8 mg/kg/day (NOAEL = 11 mg/kg/day). No other potential acute dietary endpoints for females 13-49 were found in the available database.

3.4.2 Chronic Reference Dose (cRfD)

Study Selected: Chronic toxicity study in dogs (cyfluthrin)

MRID Number: 44435401

Dose and Endpoint for Risk Assessment: 2.4 mg/kg/day (NOAEL), based on clinical signs, gait abnormalities, and abnormal postural reactions observed at 10.64 mg/kg (LOAEL)

Uncertainty Factor(s): 100X (10X for interspecies variability, 10X for intraspecies variability)

Comments about Study/Endpoint/Uncertainty Factor: This endpoint is selected from a chronic feeding study, the appropriate length and route of exposure for a chronic dietary endpoint. It is supported by the chronic feeding study in the rat (NOAEL = 2.6 mg/kg/day) and the multigeneration reproduction study in the rat (parental NOAEL = 3 mg/kg/day), where both LOAELs were based on decreased body weights.

Although the acute toxicity studies and the oral rat studies indicate that beta-cyfluthrin is more toxic than cyfluthrin and the percentages of the insecticidally active isomers in beta-cyfluthrin would indicate that it could be up to twice as toxic as cyfluthrin, it is anticipated that this endpoint would be protective for beta-cyfluthrin for the following reasons. While the oral studies in rats indicate that beta-cyfluthrin is more toxic than cyfluthrin, the oral studies in dogs (the most sensitive species for clinical signs), do not show that beta-cyfluthrin is more toxic than cyfluthrin. For example, the weight of evidence from the cyfluthrin rat studies (28-day feeding and gavage studies, subchronic feeding study, 14-day and 5-month neurotoxicity studies (gavage), chronic feeding studies and the reproduction studies) indicate that for cyfluthrin, it appears that the clinical signs of neurotoxicity in the rat may commence at a dose level somewhere between 40 and 60 mg/kg/day; whereas, in the 90-day oral study with beta-cyfluthrin, clinical signs of neurotoxicity were observed at 37.0/43.0 mg/kg/day (M/F) and in the 90-day subchronic neurotoxicity study with beta-cyfluthrin, clinical signs of neurotoxicity were observed at 27/30 mg/kg/day (M/F). In addition, examination of the developmental rat studies indicates that while the LOAEL for beta-cyfluthrin is 10 mg/kg/day (based on decreased body weights and food consumption), the LOAEL for cyfluthrin is greater than 10 mg/kg/day (although some slight effects were observed in the range-finding study at this dose level). In contrast, when all of the available dog studies are considered, the NOAEL for the 90-day dog study with beta-cyfluthrin is 2.36 mg/kg/day with gait abnormalities observed at 13.9 mg/kg/day, while the NOAELs and LOAELs from the 3 dog feeding studies conducted with cyfluthrin (one 6-month and two 12-month studies) are 5/4/2.4 (NOAELs) and 15/16/10.6 (LOAELs) mg/kg/day, respectively, based on similar effects. A comparison of these NOAELs does not indicate any major differences in toxicity between beta-cyfluthrin and cyfluthrin. A comparison of these NOAELs also does not indicate any increase in the severity of the effects over time (the NOAEL and LOAEL from the new dog study is lower because of dose spread). In addition, the NOAELs for the 28-day dog study and the 90-day dog study conducted with beta-cyfluthrin are similar. Therefore, it is unlikely that a NOAEL from a chronic dog study conducted with beta-

cyfluthrin would be less than the NOAEL for the 90-day study conducted with beta-cyfluthrin. In general, the neurological clinical signs induced by pyrethroids in dogs appear to be transient, rather than cumulative.

The NOAEL selected for the chronic RfD would be protective of any concerns to the offspring in the oral pre-and post-natal studies, including the developmental neurotoxicity study, because the NOAELs for the offspring are greater than the selected NOAEL from the chronic dog study.

3.4.3 Incidental Oral Exposure (Short- and Intermediate-Term)

Study Selected: 90-Day feeding study in dogs (beta-cyfluthrin).

MRID Number: 41267801

Dose and Endpoint for Risk Assessment: 2.36 mg/kg/day (NOAEL), based on gait abnormalities beginning in the first week, increased incidence of vomiting, and suggestive decreased body weight gain observed at 13.9 mg/kg/day (LOAEL)

Uncertainty Factor(s): 100X (10X for interspecies variability, 10X for intraspecies variability)

Comments about Study/Endpoint/Uncertainty Factor: For females, the NOAEL/LOAEL in this study is 2.5/15.4 mg/kg/day. This study is considered appropriate for short-term oral exposure (1-30 days) because it is an oral study, and gait abnormalities were observed following 3 exposures. It is supported by the chronic feeding study in the dog with cyfluthrin in which vomiting was considered to be related to treatment and was observed starting on day 1 (NOAEL 2.4 mg/kg/day). The 90-day feeding study in dogs is also supported by the acute neurotoxicity study in rats conducted with beta-cyfluthrin, a single oral dose study with a NOAEL of 2.0 mg/kg. This endpoint is also considered appropriate for intermediate-term exposure (30 days to 6 months) because it is selected from a subchronic feeding study, the appropriate length and route of exposure for intermediate incidental oral exposure.

This endpoint would be protective of any concerns to developing fetuses and/or offspring in the oral prenatal developmental, developmental neurotoxicity, and reproduction studies. No developmental effects are observed in any of these studies at dose levels in the 2.4 mg/kg/day range.

3.4.4 Dermal Absorption

Dermal Absorption Factor: 5%

No dermal penetration/absorption studies are available for cyfluthrin or beta-cyfluthrin. A conservative dermal absorption value of 5% was calculated as a comparative ratio of toxicity between the oral LOAEL of 50 mg/kg/day from a 28-day feeding study on cyfluthrin in rats and the dermal LOAEL of 1077 mg/kg/day from a 21-day (18 applications) dermal study on cyfluthrin in rats. The basis for both LOAELs included decreased food consumption; in addition, more severe toxic effects were observed in the oral study (including gait abnormalities) at the LOAEL, so the 5% dermal absorption factor is considered to be a conservative estimate.

The dermal absorption factor is required for short-, intermediate- and long-term dermal exposure assessments, since the endpoints for each of these assessments are based on oral studies.

3.4.5 Dermal Exposure (Short- and Intermediate-Term)

Study Selected: 90-Day feeding study in dogs (beta-cyfluthrin)

MRID Number: 41267801

Dose and Endpoint for Risk Assessment: 2.36 mg/kg/day (NOAEL), based on gait abnormalities (both sexes), vomiting (both sexes), and suggestive decreases in body weight gain observed in males at 13.9 mg/kg/day (LOAEL)

Uncertainty Factor(s): 100X (10X for interspecies variability, 10X for intraspecies variability)

Comments about Study/Endpoint/Uncertainty Factor: For females, the NOAEL/LOAEL in this study is 2.5/15.4 mg/kg/day. This endpoint is based on an oral study and should be used in conjunction with a 5% dermal absorption factor (section 3.3.4).

A 21-day dermal toxicity study in rats with a systemic NOAEL of 376 mg/kg/day and LOAEL of 1077 mg/kg/day was available. The LOAEL was based on decreased food consumption, red nasal discharge and urine staining, none of which are considered severely adverse, nor do they reflect the major target for cyfluthrin (clinical signs of neurotoxicity). No clinical signs of neurotoxicity were seen in this study, while such signs were seen at comparable doses following a single oral dose in rats as well as following repeated doses in dogs. Therefore, the HED did not select this study for dermal exposure risk assessments.

Instead, the HED determined that an oral study is appropriate for both short- and intermediate-term dermal exposure because the endpoints of concern (clinical signs indicative of neurotoxicity) characteristic of this compound, were seen in the most sensitive species (dog), starting after 3 exposures. In addition, this dose and endpoint are supported by similar findings in the acute neurotoxicity study with beta-cyfluthrin; the NOAEL was 2 mg/kg/day, and the LOAEL was 10 mg/kg/day based on clinical signs, changes in FOB parameters, and decreased motor activity.

This endpoint would be protective of any concerns to developing fetuses and/or offspring in the oral prenatal developmental, developmental neurotoxicity, and reproduction studies. No developmental effects are observed in any of these studies at dose levels in the 2.4 mg/kg/day range.

It was noted that following inhalation exposure, the developmental NOAEL (0.00059 mg/L, which converts to 0.16 mg/kg/day) and LOAEL (0.0011 mg/L, which converts to 0.3 mg/kg/day) are much lower than the dose (2.4 mg/kg/day) selected for this risk assessment. This would indicate that the NOAEL from the dog study would not be specifically protective of developmental effects observed in the inhalation studies. It is noted, however, that due to the significantly higher potential for absorption via the inhalation route (complete or 100%) when compared to the dermal route (5%), a direct comparison of NOAELs from inhalation studies cannot be made for dermal exposure.

3.4.6 Dermal Exposure (Long-Term)

Study Selected: Chronic toxicity study in dogs (cyfluthrin)

MRID Number: 44435401

Dose and Endpoint for Risk Assessment: 2.4 mg/kg/day (NOAEL), based on clinical signs, gait abnormalities, and abnormal postural reactions observed at 10.64 mg/kg (LOAEL)

Uncertainty Factor(s): 100X (10X for interspecies variability, 10X for intraspecies variability)

Comments about Study/Endpoint/Uncertainty Factor:

This endpoint is based on a chronic feeding study, which is the appropriate length and route of exposure for a chronic endpoint. It should be used in conjunction with a 5% dermal absorption factor (Section 3.3.4).

3.4.7 Inhalation Exposure (Short-Term)

Study Selected: 4-Week inhalation study in rats (beta-cyfluthrin)

MRID Number: 41783001

Dose and Endpoint for Risk Assessment: 0.07 mg/kg/day (0.00026 mg/L; NOAEL), based on decreases in body weight in both sexes and decreased urinary pH in males observed at 0.73 mg/kg/day (0.0027 mg/L; LOAEL)

Uncertainty Factor(s): 100X (10X for interspecies variability, 10X for intraspecies variability)

Comments about Study/Endpoint/Uncertainty Factor: This study is of appropriate duration and route for a short-term endpoint. The 90-day inhalation study of cyfluthrin in rats, which results in a lower NOAEL/LOAEL was not selected because the duration of exposure is not appropriate for a short-term endpoint. A 4-week inhalation study in rats is also available for cyfluthrin; however, it was not selected for this endpoint because the NOAEL and LOAEL in the 4-week beta-cyfluthrin inhalation study are lower and protective of effects in both 4-week studies. A 5-day inhalation study in rats with beta-cyfluthrin resulted in the same NOAEL as the 4-week study that was ultimately selected for this endpoint. Finally, there are four other inhalation studies which could have been used for this endpoint: three developmental inhalation studies and a 7-day postnatal inhalation mouse study. In all four studies, qualitative and/or quantitative increased susceptibility was observed in the offspring; however, all of the observed developmental/offspring effects are well characterized and definitive NOAELs can be established for these effects. Therefore, the degree of concern for these studies is low. The developmental NOAELs for the three developmental studies are 0.125 and 0.160 (two combined studies) mg/kg/day. The NOAEL for the postnatal mouse study is 2.48 mg/kg/day. The proposed endpoint of 0.07 mg/kg/day would be protective of these developmental/offspring NOAELs, as well as of the toxicity seen in the remainder of the toxicology database, including all oral studies.

3.4.8 Inhalation Exposure (Intermediate- and Long-Term)

Study Selected: 13-Week inhalation study in rats (cyfluthrin)

MRID Numbers: 00157793, 40082901, 40239301

Dose and Endpoint for Risk Assessment: 0.02 mg/kg/day (0.00009 mg/L; NOAEL), based on decreased body weights and body weight gains in males and clinical signs in females observed at 0.16 mg/kg/day (0.000071 mg/L; LOAEL)

Uncertainty Factor(s): 100X (10X for interspecies variability, 10X for intraspecies variability)
Comments about Study/Endpoint/Uncertainty Factor: This is a 13-week inhalation study which is the appropriate route of exposure and the appropriate time period for intermediate-term exposure. For long term exposure, an uncertainty factor for extrapolating from a subchronic study to a chronic study will not be applied because there is no evidence to show that there will be greater toxicity following longer exposure (see the chronic dietary section for a more complete discussion). In addition, this study was conducted with cyfluthrin. Although beta-cyfluthrin is more acutely toxic than cyfluthrin, an uncertainty factor for extrapolating from cyfluthrin to beta-cyfluthrin was not added. A comparison of 4-week inhalation data with cyfluthrin and beta-cyfluthrin is somewhat limited by the differences in dose spread; however, it does show that the NOAELs and LOAELs are not significantly different: the NOAEL and LOAEL for the study conducted with cyfluthrin are 0.12 and 1.6 mg/kg/day, respectively and the NOAEL and LOAEL for the study conducted with beta-cyfluthrin are 0.07 and 0.73 mg/kg/day, respectively. Both 4-week study LOAELs are based on similar effects, including body weight changes, with additional effects seen at the higher dose of 1.6 mg/kg/day in the cyfluthrin study. For further discussion on this point with the oral data, see the chronic dietary section.

The discussion on comparison with studies for which there is increased susceptibility follows the same logic as in Section 3.4.8. In addition, the proposed endpoint of 0.02 mg/kg/day is protective of the toxicity seen in the remainder of the toxicology database, including all oral studies.

3.4.9 Level of Concern for Margin of Exposure (MOE)

Table 4. Summary of Levels of Concern for Risk Assessment.			
Route	Short-Term (1 - 30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	100	100	N/A
Inhalation	100	100	N/A
Residential Exposure			
Dermal	100	100	N/A
Inhalation	100	100	N/A
Incidental Oral	100	100	N/A

3.4.10 Recommendation for Aggregate Exposure Risk Assessments

Consistent with FQPA, 1996, HED considers an aggregate risk assessment when there are potential residential exposures that may result in exposure from three major pathways (oral, dermal, and inhalation). The risks for the different routes of exposure may be aggregated due to

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the presence of a common toxicity endpoint (clinical signs of neurotoxicity and/or body weight effects).

Cyfluthrin/beta-cyfluthrin is currently registered for residential uses including indoor (e.g. total release fogger and crack and crevice spray) and outdoor uses (e.g. spray fogger, and lawn applications). Aggregate risk assessments for acute, short-term, and intermediate-term durations were conducted. In an acute aggregate risk assessment, HED combines acute dietary exposures (food + water). For a short-term aggregate risk assessment, HED combines the average dietary exposures (i.e., the chronic dietary exposures from DEEM) with the short-term residential exposure; and, for intermediate-term aggregate risk assessments, HED combines average dietary exposures (food + water) with intermediate term residential exposure. For the residential component of the cyfluthrin aggregate risk assessment, HED combined exposures from indoor carpet use and outdoor lawn use to present a conservative residential exposure scenario. Exposure pathways from both indoor carpet use and outdoor lawn use include dermal, inhalation, and oral routes for both short-term and intermediate-term durations (see HED memo D283388; S. Tadayon; 7/31/03, and HED memo; Y. Donovan; D290925; 7/15/05).

3.4.11 Classification of Carcinogenic Potential

On March 14, 1986, HED classified cyfluthrin as a Category E carcinogen (no evidence of carcinogenicity) based on the two older rat and mouse studies. Based on the new and old studies, cyfluthrin is classified as "not likely to be carcinogenic to humans" (HIARC, 2001).

3.4.12 Summary of Toxicological Doses and Endpoints for Cyfluthrin and Beta-Cyfluthrin for Use in Human Health Risk Assessments

A summary of toxicological endpoints and doses for use in the both the dietary and non-occupational risk assessment as well as the occupational assessment of cyfluthrin/beta-cyfluthrin is contained in Table 5, below.

Table 5. Toxicological Doses and Endpoints for Cyfluthrin and Beta-Cyfluthrin for Use in Non-Occupational Human Health Risk Assessments.				
Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All Populations)	NOAEL= 2 mg/kg	UF _A = 10x UF _H = 10x FQPA SF= 1x	Acute RfD = 0.02 mg/kg aPAD = 0.02 mg/kg	Acute neurotoxicity in rats (beta-cyfluthrin) LOAEL = 10 mg/kg based on clinical signs, changes in FOB parameters, and decreases in motor activity.
Chronic Dietary (All Populations)	NOAEL= 2.4 mg/kg/day	UF _A = 10x UF _H = 10x FQPA SF= 1x	Chronic RfD = 0.024 mg/kg/day cPAD = 0.024 mg/kg/day	Chronic toxicity in dogs (cyfluthrin) LOAEL = 10.64 mg/kg/day based on clinical signs, gait abnormalities, and abnormal postural reactions.

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Table 5. Toxicological Doses and Endpoints for Cyfluthrin and Beta-Cyfluthrin for Use in Non-Occupational Human Health Risk Assessments.

Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Incidental Oral Short- (1-30 Days) and Intermediate-Term (1 - 6 Months)	NOAEL= 2.36 mg/kg/day	UF _A = 10x UF _H = 10x FQPA SF= 1x	Residential LOC for MOE = 100	90-Day feeding study in dogs (beta-cyfluthrin) LOAEL = 13.9/15.4 mg/kg/day (M/F) based on gait abnormalities, increased incidence of vomiting, and suggestive decreased body weight gain.
Dermal Short- (1-30 Days) and Intermediate-Term (1 - 6 Months)	NOAEL= 2.36 mg/kg/day Dermal absorption rate = 5%	UF _A = 10x UF _H = 10x FQPA SF= 1x	Residential LOC for MOE = 100	90-Day dog feeding study (beta-cyfluthrin) LOAEL = 13.9/15.4 mg/kg/day (M/F) based on gait abnormalities, increased incidence of vomiting, and suggestive decreased body weight gain.
Dermal Long-Term (>6 Months)	NOAEL= 2.4 mg/kg/day Dermal absorption rate = 5%	UF _A = 10x UF _H = 10x FQPA SF= 1x	Residential LOC for MOE = 100	Chronic toxicity in dogs (cyfluthrin) LOAEL = 10.64 mg/kg/day based on clinical signs, gait abnormalities, and abnormal postural reactions.
Inhalation Short-Term (1-30 Days)	NOAEL= 0.00026 mg/L (0.07 mg/kg/day)	UF _A = 10x UF _H = 10x FQPA SF= 1x	Residential LOC for MOE = 100	28-Day rat inhalation study (beta-cyfluthrin) LOAEL = 0.0027 mg/L (0.73 mg/kg/day) based on decreases in body weight in both sexes and decreased urinary pH in males.
Inhalation Intermediate- (1-6 months) and Long-Term (>6 months)	NOAEL= 0.00009 mg/L (0.02 mg/kg/day)	UF _A = 10x UF _H = 10x FQPA SF= 1x	Residential LOC for MOE = 100	13-Week rat inhalation study (cyfluthrin) LOAEL = 0.00071 mg/L (0.16 mg/kg/day) based on decreases in body weight and body weight gain in males and clinical signs in females.
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans"			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

3.5 Endocrine Disruption

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect

produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA has authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, beta-cyfluthrin may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 Public Health and Pesticide Epidemiology Data

No public health data are being considered at this time.

5.0 Dietary Exposure/Risk Characterization

5.1 Metabolism and Environmental Degradation

5.1.1 Metabolism in Primary Crops

HED has concluded that the nature of cyfluthrin/beta-cyfluthrin in plants is adequately understood based on plant metabolism studies conducted in cotton, soybeans, potatoes, apples, wheat, and tomatoes. Data from those studies indicate that the nature of the residue is similar in all plant matrices. The major detected residue is the parent cyfluthrin which comprised between 38% – 98% of the total radioactive residues (TRR). In plants, cyfluthrin was seen to metabolize slowly with little translocation. Other metabolites detected, including FPBalc, FPBald, FPBacid, FPBamide, FPB methyl ester, and 4'-OH-FPBacid, generally comprised <10% of the TRR. HED, therefore, has determined that the residue of concern in plants is cyfluthrin *per se*. The nature of cyfluthrin residues in plants is summarized in the HED memorandum *Registration for Use on Grasses, Alfalfa, and Seed Treatment Use on Sugar Beets*, (D. Dotson; D339413; 10/15/2007).

5.1.2 Metabolism in Livestock

The nature of cyfluthrin/beta-cyfluthrin is adequately understood in livestock based upon metabolism data in cattle and poultry. In lactating cows the parent comprised 56-100% of the TRR in tissues and milk. In poultry, the parent comprised 28-56% of the TRR in muscle, fat, skin, and eggs, (in poultry liver and kidney, the parent comprised 9-12% of the TRR).

Metabolites (FPBalc, FPBald, FPBacid, and 4'-OH-FPBacid), comprised 0-43% of the TRR in cow tissues and milk and 0-19% of the TRR in poultry tissues and eggs. The residue of concern in animals is cyfluthrin, *per se*.

5.1.3 Analytical Methodology

Residue Analytical Method

Adequate GC/ECD methods are available in PAM Vol. II for enforcing tolerances for cyfluthrin/beta-cyfluthrin residues in/on plant commodities (Method 85823) and animal commodities (Method 85883). The limit of detection for cyfluthrin/beta-cyfluthrin in both methods is 0.01 ppm in the tested plant and animal commodities.

In the current grass, alfalfa, and sugar beet field trials, as well as the sugar beet processing study, samples were analyzed for residues of cyfluthrin using Bayer Method 108139-1 (GC/MS). This method was previously reviewed by the Agency and deemed adequate for data collection, and was adequately validated on grass, alfalfa, and sugar beet commodities in conjunction with the analysis of field trial and processing study samples.

The validated limit of quantitation (LOQ) for cyfluthrin residues in grass forage and hay is 0.05 ppm, and the statistically calculated limit of detection (LOD) is 0.014 ppm for forage, and 0.020 ppm for hay. The validated LOQ for cyfluthrin residues is 0.01 ppm for all sugar beet commodities, and the statistically calculated LODs are 0.003 ppm for tops and roots, and 0.0011-0.0018 ppm for processed fractions.

Multiresidue Method

Data pertaining to the recovery of cyfluthrin using FDA's multiresidue methods were submitted in 1998 (MRID 40355901), and forwarded to FDA. The FDA Pestrak Data Base (PAM Vol. I, Appendix, dated 11/6/90) indicates that complete recovery has been obtained for cyfluthrin using FDA multiresidue methods.

5.1.4 Environmental Degradation

Cyfluthrin is moderately persistent in the environment and immobile. Data suggest that the primary routes of dissipation include hydrolysis in alkaline media ($T_{1/2}$ = stable, essentially stable and 2.1 days at pH's 5, 7 and 9 respectively); aqueous photolysis ($T_{1/2}$ = 0.7 - 4.5 days); and, soil photolysis ($T_{1/2}$ = 5.6 days). Data indicate that aerobic soil metabolism plays a secondary role in the dissipation of cyfluthrin ($T_{1/2}$ = ranged from 73.5 and 94.8 days). Data show that cyfluthrin degrades slowly under normal conditions of aerobicity and organic matter, but degrades faster under anaerobic environments or in soils with higher organic matter. While moisture level does not appear to have a significant effect on cyfluthrin's rate of degradation, pH does (degrading faster in conditions of higher pH).

Similar to other pyrethroids, cyfluthrin is hydrophobic, binding strongly to soil surfaces. The moderate persistence of the chemical, its high soil affinity and low solubility indicate (i) a low potential to leach to subsurfaces and to contaminate groundwater; and, (ii) that the chemical has a high potential to reach surface waters in runoff events accompanied by erosion occurring during periods of weeks to months after application. Once the chemical reaches surface waters, the potential impact to water quality appears to be mostly due to parent compound. Cyfluthrin residues could also reach surface waters via spray drift.

Once cyfluthrin reaches surface waters, the potential impact to water quality appears to be mostly due to cyfluthrin, *per se*. Laboratory studies predict that once the chemical reaches surface waters, it may persist for moderate periods of time. Cyfluthrin's lipophilicity and affinity to particulate make it unavailable to photolysis. In addition, photolysis would be limited only to clear shallow waters or the upper layers of the water column.

5.1.5 Pesticide Metabolites and Degradates of Concern

The HED previously determined that the residue of concern in all matrices (plants, livestock, and drinking water) is cyfluthrin, *per se* (MARC Decision Memorandum; 6/13/02; TXR 0050805). The cyfluthrin risk assessment team is in agreement with this previous determination.

Table 6. Summary of Metabolites and Degradates to be included in the Cyfluthrin/Beta-cyfluthrin Risk Assessment and Tolerance Expression*

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
	Primary Crop	Cyfluthrin, <i>per se</i>	Cyfluthrin, <i>per se</i>
	Rotational Crop	N/A	N/A
	Ruminant	Cyfluthrin, <i>per se</i>	Cyfluthrin, <i>per se</i>
	Poultry	Cyfluthrin, <i>per se</i>	Cyfluthrin, <i>per se</i>
	Drinking Water	Cyfluthrin, <i>per se</i>	Not Applicable

* Although most of the residue from for use of beta-cyfluthrin consists of the enriched isomers of that active ingredient, low percentages of the other isomers are present and the analytical method does not distinguish between the isomers of cyfluthrin and beta-cyfluthrin. Therefore, the residue of concern from use of beta-cyfluthrin for practical purposes is cyfluthrin.

5.1.6 Drinking Water Residue Profile

Estimates of cyfluthrin residues in drinking water were provided by the Environmental Fate and Effects Division (J.L. Melendez 9/6/2007; D331952; D340739) and incorporated directly into the dietary assessment. Acute and chronic screening level estimates of drinking water concentrations (EDWCs) in surface water were generated using FIRST v.1.1.0, (Dec. 12, 2005), and ground water concentration estimates were generated using SCI-GROW v.2.3, (Jul 29, 2003).

Based on survey of all the currently registered and proposed uses of cyfluthrin, it was determined that cyfluthrin use on alfalfa and cotton would lead to the highest surface water and ground water drinking water exposure estimates (EDWCs), respectively. Based upon the proposed use of cyfluthrin on alfalfa (0.35 lb ai/acre/season), the acute drinking water concentration in surface water is 3.677 ppb, and the chronic EDWC is estimated to be 0.155 ppb. The SCI-GROW generated EDWC (in groundwater) is 0.457 ppb of cyfluthrin, which is recommended for use both for acute and chronic exposures. EDWCs are summarized in Table 7.

Table 7. Estimated Drinking Water Concentrations for Cyfluthrin/Beta-cyfluthrin			
Duration	Application Rate	Surface Water Concentration (ppb)	Groundwater Concentration (ppb)
Acute	0.35 lb ai/A/season(alfalfa)	3.677	0.457
Chronic (non-cancer)	0.50 lb. ai/A/season (cotton)	0.155	0.457

5.1.7 Food Residue Profile

5.1.7.1 Crop Field Trials

Grasses

The available field trial data for grasses adequately reflect geographic distribution, application rate, and proposed PHI. The data support the use of cyfluthrin/beta-cyfluthrin on grasses at up to four broadcast foliar applications at a maximum single application rate of 0.044 lb ai/A, with a minimum RTI of 5 days, for a maximum use rate of 0.178 lb ai/A/season. The data also support a 0-day PHI for cutting of both forage and hay. The available data support proposed tolerances of 50 ppm cyfluthrin/beta-cyfluthrin on grass hay and 12 ppm cyfluthrin/beta-cyfluthrin on grass forage.

The field trial data using the emulsifiable concentrate (EC) formulation of cyfluthrin on grasses also support the use of the WP formulation on grass, since previous side-by-side tests on numerous crops using EC and WP formulations of cyfluthrin have shown that the use of an EC formulation typically results in higher crop residues than use of a WP. Also, in accordance with an earlier HED decision the current field trial data for cyfluthrin (conducted with cyfluthrin) also support the use of beta-cyfluthrin at a maximum of 0.022 lb ai/A/application for a total use rate of 0.089 lb ai/A/season.

Alfalfa

Crop field trial data was submitted to support the use of cyfluthrin on alfalfa (EC). The highest average field trial (HAFT) value reported for cyfluthrin residue in/on alfalfa forage was 5.65 ppm (max. individual value 5.88 ppm). The HAFT value for cyfluthrin residue in/on alfalfa hay was 15.27 ppm (max. individual value 16.49 ppm). HED used the recent guidance for setting tolerances based on field trial data and determined the appropriate tolerances for alfalfa forage to be 5.0 ppm, and for alfalfa hay to be 13 ppm.

Sugar Beets

The available field trial data for sugar beet seed treatment was conducted with cyfluthrin, and adequately support the use of cyfluthrin on sugar beet seed at an application rate of 0.035 lb

ai/100,000 seeds. These data also support the use of beta/cyfluthrin at a maximum application rate of 0.017 lb ai/100,000 seeds. These data adequately reflect geographic distribution, and samples were collected at normal crop maturity. The samples were analyzed using an adequate analytical method and the sample storage durations are supported by the available storage stability data. Field trial values for both sugar beet roots and tops were below the LOQ, and as a result, HED's statistical tolerance generator was not used to determine tolerances. Therefore, HED recommends that the tolerance be set at 0.10 ppm.

Cereal Grains Except Rice (Crop Group 15)

A tolerance of 4.0 ppm is currently in effect for residues of cyfluthrin/beta-cyfluthrin in the Cereal Grain Crop Group (Group 15). This tolerance covers residues resulting from stored grain uses as well as from foliar applications. In 2004, HED recommended that the stored grain uses be cancelled (Y. Donovan, 12/16/04, D290921), but noted that cancellation of these uses should only occur after the product cleared the channels of trade. Currently, HED has reviewed field trial data that were originally reviewed between 1998 and 2004 regarding foliar applications to wheat, field corn, sweet corn, and sorghum.

Wheat

Field trial data for foliar applications to wheat were submitted and reviewed in 2004. In its 2004 review, HED recommended that the cereal grain crop group tolerance of 4.0 ppm be revoked and that a tolerance of 0.2 ppm be established in wheat grain. However, the statistically generated tolerance, which is currently required by HED policy, is 0.15 ppm. As a result, HED recommends that the wheat grain tolerance be established at 0.15 ppm (rather than the 0.2 ppm tolerance proposed in 2002). This 0.15 ppm tolerance should be extended to the following cereal grains: barley, buckwheat, millet, oats, and rye.

Field Corn

Field trial data for field corn have been submitted and reviewed. HED previously concluded that the corn grain tolerance of 0.01 ppm was adequate to cover the existing at-plant and foliar uses. However, the 0.01 ppm tolerance was not in harmonization with the Codex MRL (0.05 ppm). In 2002, HED did not recommend harmonizing the field corn grain tolerance with the Codex MRL owing to a pending stored grain use tolerance of 4.0 ppm. Since that time, the stored grain registrations have been cancelled, and as a result, HED now recommends that the field corn grain tolerance be harmonized with the Codex MRL. Therefore, HED recommends in favor of a tolerance of 0.05 ppm in field corn grain. The recommended tolerances for cyfluthrin residues on animal feed items associated with field corn are discussed below, in the section entitled *Forage, Fodder, and Straw of Cereal Grains Group Except Rice (Crop Group 16)*.

Corn

Field trial data for sweet corn were evaluated by HED in 1989 and 1995. A tolerance of 0.05 ppm was established for sweet corn, kernel plus cob with husks removed. This tolerance is currently in effect and is equivalent to the Codex MRL of 0.05 ppm in maize. HED recommends that this tolerance remain in effect. Tolerances are also in effect in sweet corn forage and stover. HED's recommendations concerning these tolerances are discussed in the section below, entitled *Forage, Fodder, and Straw of Cereal Grains Group Except Rice (Crop Group 16)*.

Sorghum

In 1996 HED recommended in favor of a 4.0 ppm tolerance for residues in sorghum grain resulting from foliar applications. In 2004, HED recommended that the sorghum grain tolerance be re-established based on pre-harvest uses of cyfluthrin. This tolerance is equivalent to the cereal grain crop group tolerance being cancelled, i.e., 4.0 ppm. However, under current HED policy, the statistically generated tolerance for sorghum grain is 3.5 ppm. The recommended tolerances for animal feed items associated with sorghum are discussed in the section below.

Rice

Rice is a member of the cereal grains crop group, and therefore, was covered by the 4.0 ppm tolerance set in that crop group. However, since these uses have been cancelled the tolerance in rice should also be removed. Since there are no further registrations for foliar application of cyfluthrin to rice, HED recommends that no new tolerance in rice be established.

Forage, Fodder, and Straw of Cereal Grains Group Except Rice (Crop Group 16)

Adequate field trial data have been submitted for wheat forage, fodder, and straw, field corn forage and fodder, sweet corn forage and stover, and sorghum forage and stover. Tolerances based upon these data are currently in effect. The registrant has requested a tolerance in Crop Group 16, the Forage, Fodder, and Hay of the Cereal Grains (Except Rice) Group, and has proposed a tolerance of 7.0 ppm in the entire crop group. Below is HED's current analysis of the data relevant to the petition for a Crop Group 16 tolerance.

Forage

Forage field trial data are available for wheat, field corn, sweet corn, and sorghum. The current tolerance in sweet corn forage is 15 ppm and is based upon field trial data submitted in 1989 and 1990. Residue values recorded in these data ranged from 2.97 ppm to 53.2 ppm. For statistical reasons, HED believed that the 53.2 ppm value was aberrant, and so based the existing 15 ppm tolerance on the next lowest value in that data set, (13.6 ppm). For the current recommendation the same data set was re-analyzed with HED's statistical tolerance generator. Based upon the result of the tolerance generator, HED recommends that the tolerance in the forage of the Cereal Grains Crop Group (Except Rice) be set at 25 ppm.

Stover

Stover field trial data are available for field corn, sweet corn, and sorghum. The individual field trial values obtained for the stover of each commodity were entered into HED's statistical tolerance generator to determine the recommended tolerance for each. As a result, HED recommends that the tolerance for the stover of the Cereal Grains Crop Group (Except Rice) be set at 30 ppm, which is the highest value of the three stover forms. A tolerance of 30 ppm is currently in effect for sweet corn stover. HED recommends that this tolerance be extended to the stover of the other cereal grains (except rice).

Hay

The only commodity for which hay field trial data are available is wheat. Based upon the statistical tolerance generator, HED recommends that this tolerance be set at 6.0 ppm and be applied to hay of the Cereal Grains Crop Group (except rice).

Straw

The only commodity for which straw field trial data are available is wheat. Based upon the statistical tolerance generator, HED recommends that this tolerance be set at 7.0 ppm and be applied to straw of the Cereal Grains Crop Group (except rice).

5.1.7.2 Revocation of Certain Tolerances

Since crop group tolerances are being established in the forage, stover, hay, and straw of the cereal grains commodities, the individual tolerances that are currently in effect should be revoked. These tolerances include the following: wheat forage (5.0 ppm), wheat hay (6.0 ppm), wheat straw (6.0 ppm), field corn forage (3.0 ppm), field corn stover (6.0 ppm), popcorn stover (6.0 ppm), sweet corn forage (15 ppm), sweet corn stover (30 ppm), sorghum grain forage (2.0 ppm), and sorghum grain stover (5.0 ppm). A Tolerance Summary table for cyfluthrin/beta-cyfluthrin can be found in Appendix C.

5.1.7.3 Processed Food and Feed

Grass

There are no regulated processed commodities associated with grass.

Sugar Beets

The available sugar beet processing study (MRID 47007810) is adequate. Using all values \geq LOD for each commodity, the processing factors were calculated to be $<0.3x$ for refined sugar, $<0.2x$ for molasses, and $12x$ for dried pulp.

Cereal Grains Crop Group Except Rice

Wheat

In 2004, HED recommended in favor of a 0.5 ppm tolerance in wheat bran. However, at that time a 6.5 ppm tolerance was established based upon the stored grains use. Since the stored grains use has been cancelled, HED recommends that the current 6.5 ppm tolerance in wheat bran be decreased to 0.5 ppm.

Corn

An acceptable field corn processing study was submitted in 2002. Even though the residues in processed commodities were not measured, HED concluded that residues would not exceed 0.01 ppm. There is a current corn oil tolerance of 30 ppm, which was established in conjunction with the stored grain uses; however, this use is being cancelled. Therefore, HED recommends that the 30 ppm tolerance be revoked. The recommended corn grain tolerance of 0.05 ppm will be adequate to cover residues in field corn, refined oil.

Rice

The current tolerances in effect for rice bran (6.0 ppm) and hulls (18.0 ppm) are derived from rice as a component of the cereal grains crop group. As mentioned above, the cereal grains

group tolerance is being cancelled. Therefore, since there are no other registrations for foliar application of cyfluthrin/beta-cyfluthrin to rice, the current tolerances for rice bran and hulls should be revoked.

5.1.7.4 International Residue Limits

Whenever possible, HED attempts to harmonize with Codex MRLs. As stated above, HED currently recommends that the field corn grain tolerance be harmonized with the Codex MRL, and set at 0.05 ppm. The current 0.05 ppm tolerance in sweet corn, kernel plus cob with husks removed is harmonized with the Codex MRL for maize. Regarding international harmonization of the proposed tolerances associated with the subject petitions (grasses, and sugar beet), there are no established or proposed Canadian, Mexican or Codex MRLs for cyfluthrin residues.

5.2 Dietary Exposure and Risk

Acute and chronic dietary exposures via food and drinking water result from the currently registered and proposed uses of cyfluthrin/beta-cyfluthrin. A full discussion of the refined dietary exposure from the registered and proposed uses of cyfluthrin/beta-cyfluthrin can be found in the HED memorandum *Cyfluthrin and Beta-Cyfluthrin Acute Probabilistic and Chronic Dietary Exposure Assessments for the Section 3 Registration Actions*, (D. Dotson; 10/15/07; D339414).

Permanent tolerances are established for residues of cyfluthrin in/on a wide variety of plant commodities at levels ranging from 0.01 ppm in/on peanuts, tree nuts, and tuberous and corn vegetables to 600 ppm in/on aspirated grain fractions (40CFR §180.436). Tolerances are also established on animal commodities at levels ranging from 0.01 ppm in eggs and poultry fat, meat, and meat byproducts to 30 ppm in milk fat; as well as a tolerance for the use of cyfluthrin in food and feed handling establishments. The Agency previously concluded that tolerances for cyfluthrin will also cover beta-cyfluthrin provided that the use rates for beta-cyfluthrin are ½ the use rates of cyfluthrin.

The current dietary analyses are refined, incorporating the most appropriate factor(s) to estimate residues of cyfluthrin/beta-cyfluthrin in/on agricultural commodities or animal commodities. Dietary residue estimates were refined using: (i) empirical and default processing factors; (ii) percent crop treated estimates and projected percent crop treated estimates; and, (iii) monitoring data. The dietary exposure estimates reflect: (i) currently registered and proposed agricultural crops; (ii) residues resulting from animal feed treatment; (iii) secondary residues from use of cyfluthrin/beta-cyfluthrin as a direct animal treatment; and, (iv) for the chronic analysis, residues resulting from treatment of food handling establishments.

5.2.1 Dietary Exposure Refinements

Processing factors were available for many of the commodities in the analysis. Various studies provided by the registrant characterize the effect (reduction or concentration) of the pesticide on a commodity as a result of various processing or preparation procedures such as washing,

juicing, drying, peeling, trimming, oil extraction, etc. When empirical processing factors were not available, default processing factors were used. Where appropriate, HED translated a processing factor from one commodity to another, and when two processing factors were available (e.g., a processing factor for washing leaf lettuce and one for washing mustard greens), HED chose the more conservative value. HED does not apply a processing factor to a commodity where monitoring data is available, since monitored commodities already reflect food preparation practices which processing factors aim to characterize. Processing factors are applicable when estimating both acute and chronic dietary exposures.

Percent crop treated values were applied to further refine residue estimates. For crops which are currently registered, percent crop treated values are taken from the USDA's National Agricultural Statistics Service. HED used projected percent crop treated values where tolerances are being proposed or where usage information is not yet available. In the acute dietary analysis, the maximum percent crop treated value is applied, whereas in the chronic analysis the average percent crop treated value is used.

Tolerances for cyfluthrin/beta-cyfluthrin exist in animal (cattle, goat, hog, poultry, and sheep) meat, meat byproducts and fat, as well as in milk and eggs. Residue values for these commodities were entered either as the established tolerance value, or refined by deriving a secondary residue estimate (which incorporates refined residue estimates on animal feed items). The current secondary residue estimates for cyfluthrin/beta-cyfluthrin also reflect updated guidance, and therefore, differs from secondary residue estimates contained in previous cyfluthrin/beta-cyfluthrin risk assessments. The secondary residue estimates from cattle (residues in tissues and in milk) reflected not only exposure to the animal via the diet but also exposure from a direct "pour-on" treatment (currently registered for application to beef and dairy cattle only). Residues resulting from both these pathways were added together in order to determine the total secondary residues in cattle commodities.

The current dietary risk assessment also reflects proposed changes to the cyfluthrin/beta-cyfluthrin tolerance expression resulting from current petitions and changes to guidance regarding livestock diets as discussed above.

5.2.2 Acute and Chronic Dietary Exposure/Risk

To calculate dietary exposure, residue estimates are coupled with consumption information. The Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID, V. 2.03) integrates consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996, and 1998. Based upon the 1994-1996, and 1998 CSFII consumption data, HED concluded that is appropriate to report risk for the following population subgroups: the general U.S. population; all infants (< 1); children 1-2; children 3-5; children 6-12; youth 13-19 adults 20-49; females 13-49; and, adults 50+ yrs old. For acute dietary scenarios, consumption data are retained as individual components whereas for chronic dietary scenarios, consumption data are averaged for the entire US population and within population subgroups. Estimated concentrations of cyfluthrin/beta-cyfluthrin in drinking water, Sec. 5.1.6, are incorporated directly into the dietary analysis. Finally, dietary exposure estimates

are compared to either the acute population adjusted dose (aPAD), or the chronic population adjusted dose (cPAD). (The aPAD and cPAD are arrived at by dividing the endpoint/dose by the appropriate uncertainty factors and FQPA factor.) Exposures that exceed 100% of the aPAD or cPAD are a risk concern to HED.

Estimated acute dietary risks for the U.S population and all population subgroups are not of concern to HED at the 99.9th percentile. Estimated chronic dietary risks for the U.S. population and all population subgroups are also not of concern to HED. The results of the chronic dietary exposure analysis are reported in Table 8.

Population Subgroup	Acute Dietary Exposure	% aPAD (99.9th Percentile)	Chronic Dietary Exposure	% cPAD
General U.S. Population	0.006378	32	0.001195	5
All Infants < 1 yr old	0.007614	38	0.002075	8.6
Children 1-2 yrs old	0.010536	53	0.004084	17
Children 3-5 yrs old	0.009869	49	0.002951	12
Children 6-12 yrs old	0.004907	25	0.001750	7.3
Youth 13-19 yrs old	0.005287	26	0.000973	4.1
Adults 20-40 yrs old	0.005390	27	0.000865	3.6
Adults 50+ yrs old	0.006398	32	0.000909	3.8
Females 13-49 yrs old	0.004788	24	0.000855	3.6

5.2.3 Cancer Dietary Risk

HED has classified cyfluthrin as “not likely to be carcinogenic to humans.” Based upon this classification, HED has determined there is insufficient hazard to warrant a cancer dietary risk assessment.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

The current petitions do not involve any residential/non-occupational uses. However, several active cyfluthrin products are registered for use at residential sites including indoor (e.g. total release fogger, and crack and crevice spray) and outdoor uses (e.g. spray fogger, and lawn applications). In 2002, HED completed an updated residential/non-occupational assessment of these uses (D283388; S. Tadayon; 7/31/02). Estimated risks from the residential/non-occupational uses were not of concern to HED. The 2002 assessment was considered screening level since it did not reflect applicable revisions to the HED Residential Exposure SOPs. Incorporation of the updated SOPs would have refined the exposure estimates and likely would have resulted in higher MOEs. Risks for the population subgroups at greatest risk, from both indoor and outdoor residential uses of cyfluthrin are summarized below in Table 9.

Table 9. Selected MOEs for Residential/Non-Occupational Uses of Cyfluthrin			
Scenario	Population Subgroup	Duration	
		Short-term duration	Intermediate-term duration
Indoor Uses (carpet use)	All infants < 1 year	1300	490
Outdoor Uses (lawn use)	All infants < 1 year	1400	920
	Adults	1600	540

6.1 Spray Drift

Spray drift is always a potential source of exposure to residents near spraying operations. This is particularly the case with aerial application but, to a lesser extent, could also be a potential source of exposure from the ground application method. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. On a chemical by chemical basis, the Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift with specific products with significant risks associated with drift.

HED notes that 0.14 lb ai/acre was the application rate used to estimate non-occupational/residential exposure from cyfluthrin/beta-cyfluthrin use on lawns. Since this rate is equal to or higher than many of the agricultural application rates, the scenario is protective of any exposure of farm children, including toddlers, via spray drift from agricultural cyfluthrin/beta-cyfluthrin applications.

7.0 Aggregate Risk Assessments and Risk Characterization

Consistent with FQPA, HED considers aggregate risk to pesticide exposures that come from three major sources: food, drinking water, and residential uses. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route (oral, dermal, and inhalation) and duration of exposure.

Based upon the non-occupational/residential uses of cyfluthrin, HED has determined that acute, short-term, intermediate-term, and chronic aggregate risk assessments are appropriate. For the short-term and intermediate-term aggregate assessments, HED combined the two potential residential exposure scenarios (indoor carpet, and outdoor lawn) for a single worst-case residential exposure component. (Estimates of exposure and risk from residential uses of cyfluthrin/beta-cyfluthrin can be found in HED document D283388; S. Tadayon; 7/31/03). For both short-term and intermediate-term scenarios, HED estimated aggregate risk to the general U.S. population, infants (< 1 year), and children (1 – 2 years).

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7.1 Acute Aggregate Risk

The acute aggregate risk is equal to dietary exposure via food and drinking water, and is identical to the exposure and risk characterized in Section 5.2.2. Acute aggregate risks for cyfluthrin/beta-cyfluthrin are less than 100% of the aPAD and therefore, do not present a risk concern to HED.

7.2 Short-Term and Intermediate-Term Aggregate Risk

To estimate short-term aggregate risk, HED combined the chronic dietary (food + water) exposures (as a measure of average dietary exposure) with the short-term residential exposure. To estimate intermediate-term aggregate risk HED combined chronic dietary (food + water) exposures with intermediate term residential exposure. Short-term and intermediate-term aggregate risks are summarized in Tables 10 and 11 below.

Population Subgroup	Average Dietary		Residential (indoor carpet + outdoor lawn) ¹						Aggregate MOE ⁶
	Dietary (food + water)		Residential Inhalation		Residential Dermal		Residential Incidental Oral		
	Exposure	MOE _{fw} ²	Exposure	MOE _i ³	Exposure	MOE _d ⁴	Exposure	MOE _o ⁵	
U.S. population	0.001195	2000	5.7E ⁻³	1200	2.5E ⁻³	940	Not assessed	Not assessed	420
Infant (<1 yr)	0.002075	1100	4.6E ⁻³	1500	1.5E ⁻³	1600	6.9E ⁻⁴	3400	400
Child (1-2 yrs)	0.004084	580	3.6E ⁻³	1900	1.4E ⁻³	1700	6.4E ⁻⁴	3700	320

¹ Individual exposure values for residential uses can be found in HED Memo; S. Tadayon; 6/31/0; D28338. Exposure values and MOEs for combined residential exposures can be found in HED Memo; Y. Donovan; 7/15/05; D290925.

² MOE_{food + water}: short-term oral NOAEL = (2.36 mg/kg/day) / chronic dietary exposure from DEEM.

³ MOE inhalation = short-term inhalation NOAEL (0.07 mg/kg/day)/residential inhalation exposure

⁴ MOE dermal = short-term dermal NOAEL (2.36 mg/kg/day)/dermal residential exposure. Dermal exposure adjusted with 5% dermal absorption factor.

⁵ MOE oral = short-term incidental oral NOAEL (2.36 mg/kg/day)/hand-to-mouth residential exposure.

⁶ Aggregate MOE (food + water + residential) =

$$\frac{1}{1/\text{MOE}_{fw} + 1/\text{MOE}_i + 1/\text{MOE}_d + 1/\text{MOE}_o}$$

Table 11. Intermediate-Term Aggregate Risk Calculations for Cyfluthrin/Beta-Cyfluthrin									
Population Subgroup	Average Dietary		Residential (indoor carpet + outdoor lawn) ¹						Aggregate MOE ⁶
	Dietary (food + water)		Residential Inhalation		Residential Dermal		Residential Incidental Oral		
	Exposure	MOE ² _{ftw}	Exposure	MOE ³ _i	Exposure	MOE ⁴ _d	Exposure	MOE ⁵ _o	
U.S. Population	0.001195	2000	5.7E ⁻⁵	350	2.5E ⁻³	940	Not assessed	Not assessed	220
Infant (<1 yr)	0.002075	1100	4.6E ⁻⁵	430	1.5E ⁻³	1600	6.9E ⁻⁴	3400	240
Child (1-2 yrs)	0.004084	580	3.6E ⁻⁵	560	1.4E ⁻³	1700	6.4E ⁻⁴	3700	230

1: Individual exposure values for residential uses can be found in HED Memo; S. Tadayon; 6/31/0; D28338. Exposure values and MOEs for combined residential exposures can be found in HED Memo; Y. Donovan; 7/15/05; D290925.

2: MOE food + water = intermediate-term oral NOAEL (2.36 mg/kg/day)/chronic dietary exposure from DEEM.

3: MOE inhalation = intermediate-term inhalation NOAEL (0.02 mg/kg/day)/residential inhalation exposure

4: MOE dermal = intermediate-term dermal NOAEL (2.36 mg/kg/day)/dermal residential exposure. Dermal exposure adjusted with 5% dermal absorption factor.

5: MOE oral = intermediate-term incidental oral NOAEL (2.36 mg/kg/day)/hand-to-mouth residential exposure.

6: Aggregate MOE (food + water + residential) =

$$\frac{1}{1/\text{MOE}_{ftw} + 1/\text{MOE}_i + 1/\text{MOE}_d + 1/\text{MOE}_o}$$

7.3 Chronic Aggregate Risk Assessment

The dietary exposure pathway (food and drinking water) is the only source of chronic exposure to cyfluthrin (i.e., 180 consecutive days or more). Therefore, the long-term aggregate exposure and risk estimates are equivalent to the chronic dietary exposure and risk estimates discussed in Section 5.2.2 above. The chronic aggregate risks for cyfluthrin are less than 100% of the cPAD for all population subgroups, and therefore, do not pose a risk concern for HED.

7.4 Cancer Aggregate Risk Assessment

Based upon HED's cancer classification of cyfluthrin and consequently the lack of hazard to warrant a cancer dietary risk assessment, a cancer aggregate risk assessment was not conducted.

8.0 Cumulative Risk Characterization/Assessment

Cyfluthrin and beta-cyfluthrin are members of the pyrethroid class of pesticides. Although all pyrethroids alter nerve function by modifying the normal biochemistry and physiology of nerve membrane sodium channels, EPA is not currently following a cumulative risk approach based on a common mechanism of toxicity for the pyrethroids. Although all pyrethroids interact with sodium channels, there are multiple types of sodium channels and it is currently unknown whether the pyrethroids have similar effects on all channels. The Agency does not have a clear understanding of effects on key downstream neuronal function e.g., nerve excitability, nor do we understand how these key events interact to produce their compound specific patterns of neurotoxicity. There is ongoing research by the EPA's Office of Research and Development and

pyrethroid registrants to evaluate the differential biochemical and physiological actions of pyrethroids in mammals. When the results of the research become available, the Agency will consider the findings and make a determination of common mechanism as a basis for assessing cumulative risk. Information regarding EPA's procedures for cumulating effects from substances found to have a common mechanism can be found on EPA's website at <http://www.epa.gov/pesticides/cumulative/>.

9.0 Occupational Exposure/Risk Pathway

A full analysis of the occupational exposure and risks associated with the proposed uses of cyfluthrin/beta-cyfluthrin can be found in the HED memorandum, *Cyfluthrin and Beta-cyfluthrin: Occupational Risk Assessment to Support the Uses of Alfalfa and Grasses and the Use of Beta-Cyfluthrin on Sugar Beet*, (September 7, 2007; D339445).

To assess occupational risks, HED compares estimated exposure to the appropriate toxicological endpoint dose. The ratio of exposure to endpoint is expressed as a margin of exposure (MOE). If the toxicological endpoint dose is equal to or greater than 100x the estimated exposure, (i.e., $MOE \geq 100$) then the risk is not of concern to HED. To estimate exposure to handlers (mixers, loaders, and applicators), HED begins by assuming baseline personal protective equipment (PPE) which is defined as long sleeve shirt, long pants, socks and shoes. If risks are of concern with baseline PPE (i.e., $MOE < 100$), then HED recalculates exposure and risk by increasing levels of PPE until the risks are not of concern to HED (i.e., $MOE \geq 100$). When estimating risk to workers who reenter treated areas, HED considers the post-application activities for a given crop, and the expected exposure from each activity to estimate risk. For handlers as well as workers who reenter fields treated with cyfluthrin/beta-cyfluthrin, HED's level of concern (LOC) is 100.

Application methods associated with the proposed uses on alfalfa and grasses include aerial/aerial ULV (by fixed wing or by helicopter), and groundboom/chemigation (sprinkler irrigation system only). Application for commercial seed treatment is with a slurry or liquid with a slurry treater or a direct treater. Commercial seed treatment also involves individuals who bag the treated seed and/or sew the bag shut. Table 12 lists the occupational exposures associated with each petition.

Table 12. Summary of Petitions and Occupational Assessments for Cyfluthrin/Beta-cyfluthrin		
Petition Description	Petition No.	Occupational Exposures Assessed
Petition for use of cyfluthrin/beta-cyfluthrin on grasses throughout the U.S. including mixed stands with alfalfa	6E7058	Exposure to handlers (mixers, loaders, applicators, flaggers) Exposure to post application workers
Petition for new use as sugar beet seed treatment	6F7160	Exposure to loader, and seed treater; Exposure to the bagger of treated seeds Exposure to the sewer of bags filled with treated seed Exposure to post treatment workers (planters)
Petition for increased number of applications to alfalfa (increased seasonal application rate)	7F7226	Exposure to handlers (mixers, loaders, applicators, flaggers) Exposure to post application workers
Request to amend labels to include Crop Group 15 (except rice) and Crop Group 16	7F7200	No occupational exposure assessments associated with this petition.

9.1 Occupational/Non-Residential Toxicological Profile for Cyfluthrin/Beta-cyfluthrin

The cyfluthrin risk assessment team has re-evaluated the cyfluthrin toxicological database and believes it continues to be sufficient to assess the occupational risks associated with the subject petitions. The cyfluthrin risk assessment team remains in agreement with the previous conclusions drawn by HED regarding the hazard of cyfluthrin. A full characterization of the hazard of cyfluthrin and beta-cyfluthrin can be found in the HED memorandum *Cyfluthrin and Beta-cyfluthrin – 3rd Report of the Hazard Identification Assessment Review Committee* (P. Hurley, TXR 0050768, 05/21/2002). Based upon the proposed uses and information regarding the production of grasses, sugar beet seed treatment, and alfalfa production, HED has determined that exposure duration for occupational handlers and applicators is short-term (1 – 30 days), and intermediate-term (1 – 6 months). Therefore, both the short-term and intermediate-term toxicity endpoints were applied in this cyfluthrin/beta-cyfluthrin occupational assessment. Table 13 summarizes the toxicological endpoints for assessing occupational/non-residential risks from cyfluthrin/beta-cyfluthrin.

Table 13. Summary of Toxicological Doses and Endpoints for Cyfluthrin and Beta-Cyfluthrin for Use in Occupational Human Health Risk Assessments.

Exposure/Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Short- (1-30 Days) and Intermediate-Term (1 - 6 Months)	NOAEL= 2.36 mg/kg/day Dermal absorption rate = 5%	UF _A = 10x UF _H = 10x	Occupational LOC for MOE = 100	90-Day dog feeding study (beta-cyfluthrin) LOAEL = 13.9/15.4 mg/kg/day (M/F) based on gait abnormalities, increased incidence of vomiting, and suggestive decreased body weight gain.
Dermal Long-Term (>6 Months)	NOAEL= 2.4 mg/kg/day Dermal absorption rate = 5%	UF _A = 10x UF _H = 10x	Occupational LOC for MOE = 100	Chronic toxicity in dogs (cyfluthrin) LOAEL = 10.64 mg/kg/day based on clinical signs, gait abnormalities, and abnormal postural reactions.
Inhalation Short-Term (1-30 Days)	NOAEL= 0.00026 mg/L (0.07 mg/kg/day)	UF _A = 10x UF _H = 10x	Occupational LOC for MOE = 100	28-Day rat inhalation study (beta-cyfluthrin) LOAEL = 0.0027 mg/L (0.73 mg/kg/day) based on decreases in body weight in both sexes and decreased urinary pH in males.
Inhalation Intermediate- (1-6 months) and Long-Term (>6 months)	NOAEL= 0.00009 mg/L (0.02 mg/kg/day)	UF _A = 10x UF _H = 10x	Occupational LOC for MOE = 100	13-Week rat inhalation study (cyfluthrin) LOAEL = 0.00071 mg/L (0.16 mg/kg/day) based on decreases in body weight and body weight gain in males and clinical signs in females.
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans"			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

9.2 Occupational/Non-Residential Exposure Inputs

No chemical specific exposure data were submitted with the subject petition for grasses, or with the petition for the increased number of applications to alfalfa. Therefore, when estimating exposure from the proposed uses on grasses, and increased rate for alfalfa, HED used surrogate data from the Pesticide Handlers Exposure Data Base (PHED) Version 1.1, and standard assessment variables established by the Health Effects Division Science Advisory Council for Exposure.

With regard to the subject petition for new use on sugar beet seed, no chemical specific data were submitted with this petition either. However, the petitioner did submit an occupational risk assessment summary (MRID 47007811) with the subject petition for sugar beet seed treatment.

A data evaluation record for this MRID was not prepared because it did not contain any original field data. Table 14 identifies the specific occupational exposure scenario combinations, including the worker population, the product formulation and equipment variations.

Table 14. Short- and Intermediate-term Occupational Exposure Scenarios Applicable for the Proposed Uses of Cyfluthrin and beta-Cyfluthrin on Alfalfa and Grasses.		
No.	Exposure Scenario	Active Ingredient
Mixing/Loading		
1	liquid, open mixing/loading for aerial, fixed wing and rotary equipment	Cyfluthrin
2	liquid, open mixing/loading for ground boom equipment	Cyfluthrin
3	liquid, open mixing/loading for chemigation	Cyfluthrin
4	WP/WSB, open mixing/loading for aerial equipment	Cyfluthrin
5	WP/WSB, open mixing/loading for ground boom equipment	Cyfluthrin
6	WP/WSB, open mixing/loading for chemigation	Cyfluthrin
7	liquid, open mixing/loading for aerial equipment	beta-Cyfluthrin
8	liquid, open mixing/loading for ground boom equipment	beta-Cyfluthrin
9	liquid, open mixing/loading for chemigation	beta-Cyfluthrin
Applying/Flagging		
10	liquid and WP, applying by aerial fixed wing equipment, enclosed cab	Cyfluthrin
11	liquid and WP, applying by aerial rotary equipment, enclosed cab	Cyfluthrin
12	liquid and WP, applying by ground boom equipment, open cab	Cyfluthrin
13	liquid and WP, flagging, aerial applications	Cyfluthrin
14	liquid, applying by aerial fixed wing equipment, enclosed cab	beta-Cyfluthrin
15	liquid, applying by aerial rotary equipment, enclosed cab	beta-Cyfluthrin
16	liquid, applying by ground boom equipment, open cab	beta-Cyfluthrin
17	liquid, flagging, aerial application	beta-Cyfluthrin

1: scenario numbers listed in Table 14 correspond with scenario numbers found in Table 1, and Table 2 in Appendix A.

9.3 Handler and Applicator Risks from Proposed Uses on Grasses and Alfalfa

The proposed labels for grasses and alfalfa specify baseline PPE (long-sleeved shirt and long pants, socks, and shoes), chemical resistant gloves, and protective eye-wear for handlers; and, specify a restricted entry interval of (REI) of 12-hours. Dermal and inhalation exposures can be combined for short and intermediate-term scenarios respectively, due to the common endpoints between these exposure routes.

Estimated risk to handlers of wettable powder/water soluble bag formulation, when using either aerial, ground boom, or chemigation equipment are not a risk concern to HED when baseline PPE is assumed. Estimated risk to handlers of liquid formulations, when using ground boom equipment, are not a risk concern to HED when baseline PPE is assumed. However, risks associated with liquid formulations when using either aerial or chemigation equipment are a concern to HED when only baseline PPE is assumed. However, when HED assumes baseline PPE, chemical resistant gloves, and a dust/mist respirator, risks were not of concern. As can be seen in Table 15, five of six handler exposure scenarios involving liquid formulations require a dust/mist respirator, (which is not indicated on the petition labels), to reach a MOE \geq 100.

Addition of a dust/mist respirator was required to bring intermediate-term inhalation exposure risks above HED's LOC of 100.

Regarding applicators and flaggers for the proposed use on grasses and on alfalfa, the short-term and intermediate-term risks are not a concern to HED when liquid or wettable powder formulations are applied via aerial, groundboom, or chemigation equipment when baseline PPE is assumed. HED notes that the proposed use directions for grasses and alfalfa require gloves which will provide additional protection to applicators and flaggers. Conclusions of handler and applicator risks and required PPE are presented in Table 15. Appendix A contains expanded tables of handler and applicator exposure and risk.

Table 15. Handlers and Applicators for Proposed Use on Grasses and Use on Alfalfa: Summary of PPE Where MOE \geq 100				
Operation	Active Ingredient	Product Formulation	Application Method	PPE Required to Reach MOE \geq 100
Handlers	Cyfluthrin	Liquid	Aerial	PPE stated on proposed label + dust/mist respirator
			Ground boom	PPE stated on proposed label + dust/mist respirator
			Chemigation	PPE stated on proposed label + dust/mist respirator
		WP/WSB	Aerial	PPE stated on proposed label
			Chemigation	PPE stated on proposed label
			Ground boom	PPE stated on proposed label
	Beta-cyfluthrin	Liquid	Aerial	PPE stated on proposed label + dust/mist respirator
			Ground boom	PPE stated on proposed label
			Chemigation	PPE stated on proposed label + dust/mist respirator
Applicators	Cyfluthrin and Beta-cyfluthrin	All formulations	All application methods	PPE stated on proposed label

9.4 Short-term and Intermediate-term Exposures and Risk from Proposed Seed Treatment Use

The proposed use pattern for sugar beet seed treatment indicates that during the seed treatment season, workers may be treating several batches of seeds per day for several weeks resulting in both short-term (1-30 days) and intermediate-term (1-6 months) exposure durations. Dermal and inhalation exposures can be combined for short and intermediate-term scenarios respectively, due to the common endpoints between these exposure routes.

The Poncho Beta® label specifies the following PPE: (i) loaders/treaters must wear long sleeved shirt and long pants, shoes with socks, chemical resistant gloves, and dust/mist respirator, (ii) baggers and sewers must wear long sleeved shirt and long pants, shoes with socks, and a dust/mist respirator. HED assessed the risk to loaders, to baggers, and to sewers separately (i.e., an individual who only loads, or only bags, or only sews), and also assessed risks to an individual who would perform all three tasks involved in seed treatment.

Risks to Individuals Performing One Discrete Task

- Short-term MOEs for all three operations do not represent a risk concern to HED.
- Intermediate-term MOEs to baggers and sewers do not represent a risk concern to HED.
- Intermediate-term MOE to loader/treaters does represent a risk concern to HED (MOE = 81).

Risks to Individuals Performing All Three Discrete Tasks

- Short-term and intermediate-term MOEs for individuals who perform all three tasks represent a risk concern to HED, (short-term MOE = 58, intermediate-term MOE = 19).

HED notes that the estimated risks to an "multiple operator" may be an overestimation because HED does not have data that accurately represents exposures from a single-person operation (including representative equipment, and/or the amount of seed that can be treated by a single person). Additional information regarding seed treatment run by a single person would be necessary to better estimate exposure and risk from this scenario. However, in the absence of more specific data, HED must rely on the data in hand which indicates that the risk to a multiple operator is a concern to HED. Conclusions of seed treatment risks and required PPE are presented in Table 16.

Table 16. Seed Treatment Operations for Proposed Use on Sugar beet Seed: Summary of Risks and PPE Where MOE \geq 100	
Operation	PPE Required to Reach MOE \geq 100
Loading, treating	<i>Intermediate-term MOE = 81 and represents a risk concern to HED Assumes PPE stated on the proposed label</i>
Bagging	PPE stated on the proposed label
Sewing	PPE stated on the proposed label
Multiple operations	<i>Risks are above HED's level of concern Short-term MOE = 58 Intermediate-term MOE = 19 Assumes PPE stated on the proposed label + chemical resistant gloves</i>

9.5 Post-application Exposure and Risk

Post-application exposure from the proposed uses of cyfluthrin/beta-cyfluthrin on grasses and alfalfa occurs when workers enter treated fields to conduct irrigation, scouting, harvesting, or other operations. Most of these post-application operations are performed using mechanical equipment, thus reducing worker exposure. Nonetheless, other post-application activities, such as scouting, are not mechanized and are expected to result in measurable exposures. HED estimated short-term and intermediate-term dermal exposure to workers who may enter

cyfluthrin and beta-cyfluthrin treated fields of alfalfa and grasses and determined that risks are not of concern (MOEs ≥ 100).

Post-application exposure from the proposed seed treatment use is likely when workers (planters) transfer the treated seeds from bags to planter-hoppers and/or while planting/drilling the seed. The estimated post-application exposures and risks (short- and intermediate-term) to planters of Poncho Beta® treated sugar beet seed are not of concern. While no PPE is required for planters while seeding/planting, HED does not anticipate direct contact with treated seed since the planting machinery places/drills the seed and covers it in one operation. Treated seeds once covered with soil are protective of workers who may reenter the field soon after planting for irrigation. No other post-application activity is performed in a freshly seeded sugar beet field. There is no restricted entry interval (REI) for the treating and planting of pre-treated seeds.

10.0 Data Needs and Label Recommendations

No data gaps were identified in the process of conducting the above analysis for the subject petitions. Based upon HED's analysis, the following label amendments are recommended to the proposed cyfluthrin/beta-cyfluthrin labels submitted in connection with the subject petitions.

Directions for Use:

- Proposed labels for use on grasses and alfalfa must be amended to exclude ultra-low volume aerial application (using a minimum of 1 qt./A of vegetable oil). No data were submitted to support this type of application, and therefore, should be removed from the proposed label.

Occupational Personal Protective Equipment:

- Addition of dust/mist respirators as a PPE requirement for all liquid formulations of Baythroid® 2, Renounce® 20WP, and Baythroid® XL.
- The intermediate-term MOE for loaders involved in the sugar beet seed treatment process is of concern to HED (intermediate-term MOE for loader/treater = 81), additional PPE may be warranted for this scenario (such as double layer clothing, or a respirator with protection factor of 10). As earlier, additional risk considerations regarding sugar beet seed treatment with Poncho Beta®, are also being addressed through a separate HED document (D340131). Together, this document and D340131 address the occupational risks associated with the proposed use of Poncho Beta® on sugar beet seed. Therefore, HED recommends the Registration Division consider the occupational risks associated with the proposed use of Poncho Beta® in light of the exposures and risks from both beta-cyfluthrin and clothianidin prior to granting the proposed use and/or tolerances associated with the proposed sugar beet seed treatment use (sugar beet roots, and sugar beet dried pulp).

New Uses:

- Pending amendments and changes HED has suggested to the proposed Baythroid® 2, Renounce® 20WP, and Baythroid® XL labels, HED recommends the registration of new uses and establishment of tolerances for cyfluthrin/beta-cyfluthrin.

Revised Tolerances for Cyfluthrin:

- HED recommends that the establishment of tolerances incorporates the correct commodity definitions for cyfluthrin (and beta-cyfluthrin) treated commodities as stated in Appendix C, Table 1 and in the *Summary of Recommendations*.

Revised Section F:

- A revised Section F is required reflecting HED recommendations, and for the establishment of (separate) tolerances listed below for both cyfluthrin and beta-cyfluthrin. The cyfluthrin tolerances should be included in 40 CFR §180.436(a)(1), while a separate section under 180.436 should be established for tolerances for beta-cyfluthrin, analogous to the tolerances for lambda-cyhalothrin and gamma-cyhalothrin in §180.438. The section for beta-cyfluthrin needs to be established because registrations for cyfluthrin on these commodities might be cancelled at some point in the future. The tolerances for cyfluthrin and beta-cyfluthrin should be established at the same levels. The recommended wording for the beta-cyfluthrin tolerance expression is as follows: "Tolerances are established for residues of the insecticide beta-cyfluthrin [mixture comprising the enantiomeric pair (R)- α -cyano-4-fluoro-3-phenoxybenzyl (1S,3S)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate and (S)- α -cyano-4-fluoro-3-phenoxybenzyl (1R,3R)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate with the enantiomeric pair (R)- α -cyano-4-fluoro-3-phenoxybenzyl (1S,3R)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate and (S)- α -cyano-4-fluoro-3-phenoxybenzyl (1R,3S)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate] in or on the following commodities:"
- HED also recommends that, at some point in the future, tolerances be established for all food uses of beta-cyfluthrin (i.e., on those commodities not included in the present actions) under the new section to be created under 40 CFR §180.436.

Appendix A. Occupational Exposure and Risk Tables

Chemical	Mixing/Loading Exposure Scenario #	PPE ¹	Dermal Unit Exposure (mg/lb ai)	Inhalation Unit Exposure (µg/lb ai)	Dermal Dose (mg/kg/day) ²	Inhal Dose (mg/kg/day) ³	Total Short-term MOE ⁴	Total Intermediate-term MOE ⁴
Cyfluthrin	1. Liquid, Open, Aerial	BL	2.9	1.2	0.109371	0.000905	17	11
"	1a. " "	BL+G+R	0.023	0.24*	0.000867	0.000181	340	110
"	2. Liquid, Open, Ground boom	BL	2.9	1.2	0.018229	0.000151	100	66
"	2a. " "	BL+G+R	2.9	0.24*	0.018229	0.000030	120	110
"	3. Liquid, Open, Chemigation	BL	2.9	1.2	0.031900	0.000264	58	37
"	3a. " "	BL+G+R	0.023	0.24*	0.000253	0.000053	1,200	360
"	4. WP/WSB, Open, Aerial	BL	0.021	0.24	0.000792	0.000181	340	110
"	5. WP/WSB, Open, Ground boom	BL	0.021	0.24	0.000132	0.000030	2,100	640
"	6. WP/WSB, Open, Chemigation	BL	0.021	0.24	0.000231	0.000053	1,200	370
Beta-cyfluthrin	7. Liquid, Open, Aerial	BL	2.9	1.2	0.054686	0.000453	34	22
"	7a. " "	BL+G+R	0.023	0.24*	0.000434	0.000091	680	210
"	8. Liquid, Open, Ground boom	BL	2.9	1.2	0.009114	0.000075	200	130
"	9. Liquid, Open, Chemigation	BL	2.9	1.2	0.015950	0.000132	120	75
"	9a. " "	BL+G+R	2.9	0.24*	0.015950	0.000026	140	120

1. BL = baseline PPE (long-sleeve shirt, long pants, shoes with socks, and no respirator), G = Gloves, R = dust-mist respirator.

2. Dermal dose/day = (app. rate)(area treated/day)(dermal unit exposure)(dermal absorption factor)(conversion factor [0.01]) ÷ body weight

3. Inhalation dose/day = (app. rate)(area treated/day)(inhalation unit exposure)(conversion factor [0.01]) ÷ body weight

4. Total Short-term or Total Intermediate-term MOE: $1 \div 1/\text{dermal MOE} + 1/\text{inhalation MOE}$

*. Applied an 80% reduction factor to the inhalation unit exposures for the use of dust/mist respirator as a mitigation measure. Ref: Exposure mitigating Table (PHED).

Table 7. Short- and Intermediate-term Occupational Risks to Applicators From the Use of Cyfluthrin and <i>beta</i> -Cyfluthrin on Alfalfa and Grasses								
Chemical	Mixing/Loading Exposure Scenario #	PPE ¹	Dermal Unit Exposure (mg/lb ai)	Inhalation Unit Exp (µg/lb ai)	Dermal Dose (mg/kg/day) ²	Inhal. Dose (mg/kg/day) ³	Total Short-term MOE ⁴	Total Inter-term MOE ⁴
Cyfluthrin	10. Liquid & WP, Aerial, Fixed wing, Enclosed cab	BL	0.005	0.068	0.000189	0.000051	1,200	380
"	11. Liquid & WP, Aerial, Rotary, Enclosed cab	BL	0.0019	0.0018	0.000072	0.0000014	20,000	10,000
"	12. Liquid & WP, Gr, boom, Open cab	BL	0.014	0.74	0.000088	0.000093	730	210
"	13. Liquid & WP, Aerial, Flagger	BL	0.011	0.35	0.000121	0.000077	870	260
<i>Beta</i> -cyfluthrin	14. Liquid & WP, Aerial, Fixed Wing, Enclosed cab	BL	0.005	0.068	0.000094	0.000026	2,500	760
"	15. Liquid & WP, Aerial, Rotary, Enclosed cab	BL	0.0019	0.0018	0.000036	0.000001	40,000	20,000
"	16. Liquid & WP, Gr, boom, Open cab	BL	0.014	0.74	0.000044	0.000047	1,500	430
"	17. Liquid & WP, Aerial, Flagger	BL	0.011	0.35	0.000061	0.000039	1,700	510

1. BL = baseline PPE, G = Gloves, R = dust/mist respirator; baseline PPE consists of long-sleeve shirt, long pants, shoes with socks and no respirator.

2. Dermal dose/day = (app. rate)(area treated/day)(dermal unit exposure)(dermal absorption factor)(conversion factor [0.01]) ÷ body weight

3. Inhalation dose/day = (app. rate)(area treated/day)(inhalation unit exposure)(conversion factor [0.01]) ÷ body weight

4. Total Short-term or Total Intermediate-term MOE: $1 \div 1/\text{dermal MOE} + 1/\text{inhalation MOE}$

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Table 10. Short- and Intermediate-Term Postapplication Risks to Workers Who Enter Alfalfa and Grass Fields Treated with Cyfluthrin and beta-Cyfluthrin.						
Crops ¹	Chemical	Max. Single Appl. Rate (lb ai/A)	DFR µg/cm ²	Transfer Coefficient ³	Dermal Dose (mg/kg/day) ⁴	Short- & Inter-term MOE ⁵
Alfalfa and Grass grown for seed	cyfluthrin	0.044	0.099	1500 scouting	0.00085	2,800
	beta-cyfluthrin	0.022	0.049	1500 scouting	0.00042	5,600

1. Among the grass crop sites (pasture, rangeland, grasses grown for hay and seed, grass mixed-stands with alfalfa), grass grown for seed is expected to have the maximum postapplication activities.

2. DFR :

(app. rate)(fraction of ai retained on foliage [20%])(fraction of residue that dissipates daily [10%])(conversion factor [4.54 E+8][2.47E-8])

3. Transfer coefficient (TC) is for alfalfa (surrogate crop) with medium exposure potential.

4. Dermal Dose: (dislodgeable foliar residue on designated day)(conversion factor [10E-3])(transfer coefficient)(dermal absorption factor)(exposure time [8 hrs]) ÷ body weight

5. Dermal MOE: NOAEL/dermal dose

Exposure Scenarios	Worker Type	PPE ²	Qty Treated/Planted/day (lbs)	Unit Exp Dermal/day (mg/lb ai)	Unit Exp Inhal/day (µg/lb ai)	Dermal Dose/day (mg/kg)	Inhalation Dose/day (mg/kg)	Total Short-term MOE ³	Total Inter-term MOE ⁵
Loading/Treating	L/T	S, G	52,000	0.023	0.34	0.00365	0.00108	59	18
Loading/Treating	L/T	S, G, R	52,000	0.023	0.068 *	0.00365	0.00022	220	81
Bagging, treated seed	Bagger	S	52,000	0.0091	0.16	0.00144	0.00051	130	38
Bagging, treated seed	Bagger	S, R	52,000	0.0091	0.032 *	0.00144	0.00010	490	180
Sewing, bagged seed	Sewer	S	52,000	0.0062	0.23	0.00098	0.00073	92	27
Sewing, bagged seed	Sewer	S, R	52,000	0.0062	0.046 *	0.00098	0.00015	400	130
Doing multiple jobs	Multiple	S, G	52,000	0.0420	1.6	0.00666	0.00508	13	4
Doing multiple jobs	Multiple	S, G, R	52,000	0.0420	0.32 *	0.00666	0.00102	58	19
Handling/ Planting ⁶	Farmer, Postappl.	S, #	640	0.25	3.4	0.00049	0.00013	470	150

2. S = Single layer (long sleeve shirt and long pants) and no gloves, G = chemical resistant gloves, R = dust/mist respirator

3. Dermal dose = (app. rate)(area treated/day)/(dermal unit exposure)(dermal absorption factor)(conversion factor [0.01]) ÷ body weight

4. Inhalation dose = (app. rate)(area treated/day)(inhalation unit exposure)(conversion factor [0.01]) ÷ body weight

5. Total Short-term or Total Intermediate-term MOE: $1 \div 1/\text{dermal MOE} + 1/\text{inhalation MOE}$

6. Postapplication exposure.

* Applied an 80% reduction factor to the inhalation unit exposure for the use of dust/mist respirator, which is a PPE requirement on the label for all seed treatment workers. Ref: Exposure Mitigating Table (PHED).

#. For handlers/planters, label specifies gloves for loading only.

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Appendix B. Toxicology Profile of Cyfluthrin and Beta-cyfluthrin

The requirements (40 CFR 158.340) for food uses for beta-cyfluthrin are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Appendix B, Table 1			
Toxicology Data Requirements – cyfluthrin/beta-cyfluthrin			
Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	-
870.3465	90-Day Inhalation	no	yes
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes ¹
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations ..	yes	yes
870.5550	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	yes	yes
870.6100b	90-Day Neurotoxicity (hen)	no	-
870.6200a	Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b	90-Day Neurotox. Screening Battery (rat)	yes	yes
870.6300	Developmental Neurotoxicity	yes	yes
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	no	-

¹ Satisfied with combined chronic toxicity/carcinogenicity study

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Appendix B Toxicology Profile of Cyfluthrin and Beta-cyfluthrin

Appendix B, Table 2 Acute Toxicity Profile – Cyfluthrin				
Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral – rat	00131499 00131518	In cremophor LD ₅₀ = 16.2 mg/kg (♂)	I
			In acetone LD ₅₀ = 254 mg/kg (♂)	II
			In N-methyl pyrrolidone LD ₅₀ = 500 -1000 mg/kg (♂)	III
870.1200	Acute dermal – rat	00131499 00131518	In cremophor LD ₅₀ > 5000 mg/kg (♂+♀) In 0.9% NaCl LD ₅₀ > 5000 mg/kg (♂+♀) Undiluted LD ₅₀ > 5000 mg/kg (♂+♀)	IV
870.1300	Acute inhalation – rat	00131509	Aqueous cremophor LC ₅₀ > 0.735 mg/L (♂) LC ₅₀ = 0.468 mg/L (♀) DMSO/polyethylene glycol LC ₅₀ = 0.575 mg/L (♂) LC ₅₀ = 0.490 mg/L (♀)	II
870.2400	Acute eye irritation – rabbit	00131499	No corneal opacity; transient irritation for 3 days	III
870.2500	Acute dermal irritation – rabbit	00131499	Non-irritating. Primary irritation score = 0	IV
870.2600	Skin sensitization – guinea pig	00131512	Not a sensitizer (Draize test)	N/A
		00131513	Not a sensitizer (Maximization test)	

Appendix B Toxicology Profile of Cyfluthrin and Beta-cyfluthrin

Appendix B, Table 3				
Acute Toxicity Profile – Beta-Cyfluthrin				
Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral – rat	41244101	In xylene Fasted: LD ₅₀ = 211 mg/kg (♂) LD ₅₀ = 336 mg/kg (♀) Fed: LD ₅₀ = 307 mg/kg (♂) LD ₅₀ = 343 mg/kg (♀)	II
870.1100	Acute oral – rat	41244102	In PEG 400 Fasted: LD ₅₀ = 380 mg/kg (♂) LD ₅₀ = 651 mg/kg (♀) Fed: LD ₅₀ = 655 mg/kg (♂) LD ₅₀ = 1369 mg/kg (♀)	II (♂) III (♀)
870.1100	Acute oral – rat	41244104	In acetone/peanut oil Fasted: LD ₅₀ = 84 mg/kg (♂) LD ₅₀ = 77 mg/kg (♀) Fed: LD ₅₀ = 141 mg/kg (♂) LD ₅₀ = 108 mg/kg (♀)	II
870.1100	Acute oral – mouse	41244103	In PEG 400 Fasted: LD ₅₀ = 91 mg/kg (♂) LD ₅₀ = 165 mg/kg (♀)	II
870.1200	Acute dermal – rat	41244105	In xylene LD ₅₀ > 5000 mg/kg (♂) LD ₅₀ > 5000 mg/kg (♀)	IV
870.1200	Acute dermal – rat	41244106	In PEG 400 LD ₅₀ > 5000 mg/kg (♂) LD ₅₀ > 5000 mg/kg (♀)	IV
870.1300	Acute inhalation – rat	41205701	Aerosol LC ₅₀ = 0.081-0.082 mg/L (♂+♀) Dust LC ₅₀ = 0.532 mg/L (♂+♀)	II III
870.2400	Acute eye irritation – rabbit	41205702	Slight ocular irritant	III
870.2500	Acute dermal irritation – rabbit	41205702	Very slight dermal irritant	IV
870.2600	Skin sensitization – guinea pig	43611601	Not a sensitizer; however, positive control data not available	N/A

Appendix B Toxicology Profile of Cyfluthrin and Beta-cyfluthrin

Appendix B, Table 4 Subchronic, Chronic and Other Toxicity Profile – Cyfluthrin and Beta-Cyfluthrin			
Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100	90-Day oral toxicity (rat) Beta-cyfluthrin (99.7% a.i.)	41244108 (1986) Acceptable/guideline M: 0, 2.3, 9.5, 18.9 mg/kg/day F: 0, 2.5, 10.9, 42.4 mg/kg/day M: 0, 37.0 mg/kg/day F: 0, 43.0 mg/kg/day	NOAEL = 9.5/10.9 mg/kg/day (M/F) LOAEL = 37.0/43.0 mg/kg/day (M/F) based on gait abnormalities, necrosis in head and neck region, mortality (2), decreased body weight gain.
870.3100	90-Day oral toxicity (rat) Cyfluthrin (84.2% a.i.)	00131524 (1980) Unacceptable/guideline M: 0, 2.2, 7.4, 22.3 mg/kg/day F: 0, 2.7, 8.8, 28.0 mg/kg/day	NOAEL = 22.3/28.0 mg/kg/day (M/F) LOAEL = not observed
870.3150	90-Day oral toxicity (dog) Beta-cyfluthrin (99% a.i.)	41267801 (1987) Acceptable/guideline M: 0, 0.39, 2.36, 13.9 mg/kg/day F: 0, 0.39, 2.5, 15.4 mg/kg/day	NOAEL = 2.36/2.5 mg/kg/day (M/F) LOAEL = 13.9/15.4 mg/kg/day (M/F) based on gait abnormalities (both sexes), vomiting (both sexes) and suggestive decrease in body weight gain.
870.3200	21/28-Day dermal toxicity (rat) Cyfluthrin (≥95.5%)	44066001 (1996) Acceptable/guideline 0, 113, 376, 1077 mg/kg/day In acetone, 6 hrs/day, for 18 applications within 23 days (♂) or 17 applications within 22 days (♀)	Dermal NOAEL = 113 mg/kg/day Dermal LOAEL = 376 mg/kg/day based on gross and histological skin lesions. Systemic NOAEL = 376 mg/kg/day Systemic LOAEL = 1077 mg/kg/day based on decreased food consumption, red nasal discharge and urine staining.
Non-guideline	28-Day oral toxicity (rat) Cyfluthrin	00131525 (1983) Supplementary 0, 5, 15, 50 mg/kg/day	NOAEL = 15 mg/kg/day LOAEL = 50 mg/kg/day based on gait abnormalities, salivation, nervousness, decrease in body weight, food consumption, changes in hematological, clinical chem. & urinalysis parameters, increases in selected organ wts., cytoplasmic swelling of glandular epithelium of submaxillary gland, minimal degrees of fiber degeneration in sciatic nerve (# not reported) which disappeared after recovery period. <i>Note: The NOAEL was changed to 15 mg/kg/day and the LOAEL to 50 mg/kg/day by the HIARC (May 21, 2002 report).</i>
870.3465	90-Day inhalation toxicity (rat) Cyfluthrin (94.9% a.i.)	00157793 (1984), 40082901, 40239301 Acceptable/guideline 0, 0.00009, 0.00071, 0.00451 mg/L	NOAEL = 0.00009 mg/L (0.02 mg/kg/day) LOAEL = 0.00071 mg/L (0.16 mg/kg/day) based on decreased body weights and body weight gains in males and clinical signs in females.

Appendix B, Table 4 Subchronic, Chronic and Other Toxicity Profile – Cyfluthrin and Beta-Cyfluthrin			
Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
		(0, 0.02, 0.16, 0.91 mg/kg/day) In ethanol/PEG 400 (1:1), 6 hrs/day, 5 consecutive days/week	
Non-guideline	4-Week inhalation toxicity (rat) Cyfluthrin (93.8% a.i.)	41842601 (1989) Acceptable/non-guideline 0, 0.00044, 0.006, 0.047 mg/L (0, 0.12, 1.6, 12.8 mg/kg/day) In ethanol/PEG 400 (1:1), 6 hrs/day, 5 consecutive days/week	NOAEL = 0.00044 mg/L (0.12 mg/kg/day) LOAEL = 0.006 mg/L (1.6 mg/kg/day) based on decreases in body weight and body weight gain in males, hypothermia, reduction in leukocyte counts (F) and low serum protein.
Non-guideline	4-Week inhalation toxicity (rat) Beta-cyfluthrin (97.9% a.i.)	41783001 (1989) Acceptable/non-guideline 0, 0.00026, 0.0027, 0.023 mg/L (0, 0.07, 0.73, 6.3 mg/kg/day) In ethanol/PEG 400 (1:1), 6 hrs/day, 5 consecutive days/week	NOAEL = 0.00026 mg/L (0.07 mg/kg/day) LOAEL = 0.0027 mg/L (0.73 mg/kg/day) based on decreased body weights, ↓ urine pH in males.
Non-guideline	5-Day inhalation study (rat) Beta-cyfluthrin (98% a.i.)	41205708 (1988) Acceptable/non-guideline 0, 0.00025, 0.0038, 0.028 mg/L (0, 0.07, 1.03, 7.6 mg/kg/day) In ethanol/PEG 400 (1:1), 6 hrs/day	NOAEL = 0.00025 mg/L (0.07 mg/kg/day) LOAEL = 0.0038 mg/L (1.03 mg/kg/day) based on unpreened hair coat, piloerection, hepatoid foci in lungs.
Non-guideline	28-Day oral toxicity (dog) Beta-cyfluthrin	41244109 (1986) Acceptable/non-guideline 0, 0.25, 2.0, 16.0/8.0 mg/kg/day (2 dogs/sex/dose)	NOAEL = 2.0 mg/kg/day (both sexes) LOAEL = 8.0 mg/kg/day based on impaired movement and conjunctival irritation.

Appendix B, Table 4 Subchronic, Chronic and Other Toxicity Profile – Cyfluthrin and Beta-Cyfluthrin			
Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.3700a	Prenatal oral developmental toxicity in rodents (rat) Beta-cyfluthrin (96.5-97.3% a.i.)	44116501 (1996) Acceptable/guideline 0, 3, 10, 40 mg/kg/day 1% Cremophor in municipal tap water	Maternal NOAEL = 3 mg/kg/day Maternal LOAEL = 10 mg/kg/day based on reduced body weight gain and reduced food consumption with post-treatment recovery. Developmental NOAEL = 10 mg/kg/day Developmental LOAEL = 40 mg/kg/day based on reduced fetal body weights and increased skeletal variations.
870.3700a	Prenatal oral developmental toxicity in rodents (rat) Cyfluthrin (93.4%)	00157794 (1983) Unacceptable/guideline 0, 1, 3, 10 mg/kg/day 1% Cremophor EL in distilled water	Maternal NOAEL = 10 mg/kg/day Maternal LOAEL = not observed Developmental NOAEL = 10 mg/kg/day Developmental LOAEL = not observed
870.3700b	Prenatal oral developmental toxicity in non-rodents (rabbit) Cyfluthrin (96% a.i.)	42675401 (1992) Acceptable/guideline 0, 20, 60, 180 mg/kg/day In corn oil, by gavage	Maternal NOAEL = 20 mg/kg/day Maternal LOAEL = 60 mg/kg/day based on decreased body weight gain and food consumption during the dosing period. Developmental NOAEL = 180 mg/kg/day Developmental LOAEL = not observed
870.3700a	Prenatal inhalation developmental toxicity in rodents (rat) Cyfluthrin (96.2% a.i.)	43393401 (1991-1994) Acceptable/guideline 0, 0.00046, 0.00255, 0.0119, 0.0128 mg/L/day (0.125, 0.692, 3.234, 3.478 mg/kg/day) In PEG-400:ethanol for 6 hrs/day	Maternal NOAEL = not determined Maternal LOAEL = 0.00046 mg/L (0.125 mg/kg/day) based on decreased body weight gain and relative food efficiency. Developmental NOAEL = 0.00046 mg/L (0.125 mg/kg/day) Developmental LOAEL = 0.00255 mg/L (0.692 mg/kg/day) based on reduced fetal and placental weights and reduced ossification in phalanx, metacarpals, vertebrae.
870.3700a	Prenatal inhalation developmental toxicity in rodents (rat) Cyfluthrin (92.9% and 93%)	40780401 (1988) Acceptable/guideline 1. 0, 0.0011, 0.0047, 0.0237 mg/L/day (0, 0.299, 1.277, 6.44 mg/kg/day) 2. 0, 0.00009, 0.00025, 0.00059, 0.0042 mg/L/day (0, 0.0245, 0.0679, 0.160, 1.141 mg/kg/day) Dissolved in a 1:1 mixture of Lutrol and ethanol for 6 hrs/day.	Maternal NOAEL = 0.0011 mg/L (0.299 mg/kg/day) Maternal LOAEL = 0.0047 mg/L (1.277 mg/kg/day) based on reduced motility, dyspnea, piloerection, ungroomed coats, eye irritation. Developmental NOAEL = 0.00059 mg/L (0.160 mg/kg/day) Developmental LOAEL = 0.0011 mg/L (0.299 mg/kg/day) based on increased incidence of runts and skeletal anomalies in sternum.

Appendix B, Table 4

Subchronic, Chronic and Other Toxicity Profile – Cyfluthrin and Beta-Cyfluthrin

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
Non-guideline	7-Day postnatal inhalation study (pups & dams) in mice with spontaneous motor activity measurements Cyfluthrin (96.8% a.i.)	44373401 (1997) Acceptable/non-guideline 0, 0.006, 0.015, 0.058 mg/L (0, 2.48, 6.21, 24.0 mg/kg/day) In PEG 400, 6 hrs/day, for 7 consecutive days	Maternal NOAEL = 0.058 mg/L (24.0 mg/kg/day) Maternal LOAEL = not determined Offspring NOAEL = 0.006 mg/L (2.48 mg/kg/day) Offspring LOAEL = 0.015 mg/L (6.21 mg/kg/day) based on clinical signs of toxicity and spontaneous motor activity observed in females 4 months after exposure.
870.3800	Reproduction and fertility effects (rat) Cyfluthrin (95.4% a.i.), corn oil/acetone premix	44371401 (1996) Acceptable/guideline Premating and gestation: M: 0, 3, 9, 29 mg/kg/day F: 0, 4, 10, 33 mg/kg/day First 2 weeks of lactation: 0, 7, 19, 59 mg/kg/day	Parental/Systemic NOAEL = 3/4 mg/kg/day (M/F) Parental/Systemic LOAEL = 9/10 mg/kg/day (M/F) based on reductions in body weights and food consumption. Offspring NOAEL = 7 mg/kg/day (M/F) Offspring LOAEL = 19 mg/kg/day based on coarse tremors in pups during lactation and decreases in mean litter weight.
Non-guideline	“Supplemental” 2-generation reproduction study (rat) Cyfluthrin (95.5% a.i.)	44371402 (1997) Acceptable/non-guideline M: 0, 1.9, 3.8 mg/kg/day F: 0, 2.1, 4.2 mg/kg/day Corn oil/acetone premix	Parental/Systemic NOAEL = 3.8/4.2 mg/kg/day (M/F) Parental/Systemic LOAEL = not determined Offspring NOAEL = 3.8/4.2 mg/kg/day (M/F) Offspring LOAEL = not determined
Non-guideline	Pilot one-generation reproduction study (rat) Cyfluthrin (95.7-96.2% a.i.), corn oil/acetone premix	43792901 (1995) Acceptable/non-guideline M: 0, 3.4, 9.3, 24.2, 38.9 mg/kg/day F: 0, 4.1, 10.5, 27.2, 43.9 mg/kg/day Gestation: 0, 3.9, 10.1, 27.2, 45.0 mg/kg/day Lactation: 0, 7.8, 22.9, 59.6, 95.9 mg/kg/day	Parental/Systemic NOAEL = 22.9 mg/kg/day Parental/Systemic LOAEL = 59.6 mg/kg/day based on hind leg splay, ataxia, reduction in body weight gain. Offspring NOAEL = 7.8 mg/kg/day Offspring LOAEL = 22.9 mg/kg/day based on tremors during lactation and pup weight decreases. Dosages for the NOAEL and LOAEL calculated from weekly mean test material consumption during lactation because both the large variation in consumption values and the increased test material consumption during the time that the effects were noted.

Appendix B, Table 4 Subchronic, Chronic and Other Toxicity Profile – Cyfluthrin and Beta-Cyfluthrin			
Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.3800	Reproduction and fertility effects (rat) (1983) Cyfluthrin	00131532 (1983) Acceptable M: 0, 3.8, 12.3, 37.2 mg/kg/day F: 0, 5.4, 15.1, 48.5 mg/kg/day This study was classified core minimum, although it had a number of deficiencies: test article 50% premix with Wessalon S, no individual litter observations, limited necropsy & histopathology, other reporting deficiencies.	Parental/Systemic NOAEL = 12.3/15.1 mg/kg/day (M/F) Parental/Systemic LOAEL = 37.2/48.5 mg/kg/day (M/F) based on decreased body weight gain. Offspring NOAEL = 5.4 mg/kg/day Offspring LOAEL = 15.1 mg/kg/day based on decreased viability during lactation period and decreased body weight gains.
870.4100b	Chronic toxicity (dog) Cyfluthrin (94.9-95.1% a.i.)	44435401 (1997) Acceptable/guideline M: 0, 1.36, 2.43, 10.64, 15.47 mg/kg/day F: 0, 1.46, 3.61, 10.74, 17.99 mg/kg/day Corn oil premix	NOAEL = 2.43/3.61 mg/kg/day (M/F) LOAEL = 10.64/10.74 mg/kg/day (M/F) based on clinical signs, gait abnormalities, and abnormal postural reactions in males and females.
870.4100b	Chronic toxicity (dog) Cyfluthrin	00151358 (1983) Core minimum 0, 1, 4, 16 mg/kg/day 50% premix with Wessalon S	NOAEL = 4.0 mg/kg/day LOAEL = 16.0 mg/kg/day based on gait abnormalities, vomiting, liquid feces, decreased body weights (males).
870.4100b	6-Month oral toxicity (dog) Cyfluthrin	00131530 (1981) Core minimum 0, 1.62, 5, 15 mg/kg/day	NOAEL = 5.0 mg/kg/day LOAEL = 15.0 mg/kg/day based on gait abnormalities, arching backs, vomiting, diarrhea.
870.4200	Carcinogenicity (mouse) Cyfluthrin (≥93.9% a.i.)	44589701 (1998) Acceptable/guideline M: 0, 31.9, 114.8, 232.7 mg/kg/day F: 0, 38.4, 140.6, 309.7 mg/kg/day Corn oil premix	NOAEL = 31.9/140.6 mg/kg/day (M/F) LOAEL = 114.8 mg/kg/day (M) based on ear skin lesions and reduced body weight gains. 309.7 mg/kg/day (F) based on clinical signs, macroscopic and microscopic pathology findings, and reduced body weights, body weight gains, and food consumption. <i>No evidence of carcinogenicity</i>

Appendix B, Table 4 Subchronic, Chronic and Other Toxicity Profile – Cyfluthrin and Beta-Cyfluthrin			
Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.4200	Carcinogenicity (mouse) Cyfluthrin (49.7-51.0% a.i.)	00137304 (1983) Acceptable/guideline M: 0, 11.6, 45.8, 194.5 mg/kg/day F: 0, 15.3, 63.0, 259.9 mg/kg/day Premix in Wessalon S	Study not acceptable for chronic toxicity. <i>No evidence of carcinogenicity</i>
870.4300	Combined chronic feeding/ carcinogenicity (rat) Cyfluthrin (94.7% a.i.),	44459301 (1997) Acceptable/guideline M: 0, 2.6, 11.6, 22.8 mg/kg/day F: 0, 3.3, 14.4, 28.3 mg/kg/day Acetone/corn oil pre-mix	NOAEL = 2.6/3.3 mg/kg/day (M/F) LOAEL = 11.6/14.4 mg/kg/day (M/F) based on overall declines in body weight gain by 12 and 10% in males and females, respectively. <i>No evidence of carcinogenicity</i>
870.4300	Combined chronic feeding/ carcinogenicity (rat) Cyfluthrin (49.7-51.0% purity as a premix concentrate in Wessalon S)	00137303 (1983) Acceptable/guideline M: 0, 2.02, 6.19, 19.20 mg/kg/day F: 0, 2.71, 8.15, 25.47 mg/kg/day	NOAEL = 6.19/8.15 mg/kg/day (M/F) LOAEL = 19.20/25.47 mg/kg/day (M/F) based on decreased body weights and body weight gains. <i>No evidence of carcinogenicity</i>
870.5100	Gene mutation – bacterial reverse mutation assay Cyfluthrin	00131539 (1982) Acceptable/guideline 5-5000 ug/plate	Negative. No increases in reverse mutations with and without activation.
870.5100	Gene mutation – yeast reverse mutation assay Cyfluthrin	00131541, 00144017 (1982) Acceptable/guideline 312.5-1000 ug/mL	Negative. No increase in number of revertants with S138 cultures. Increase in number of revertants with S211 culture but not dose-related; no increase in number of revertants when assay repeated.
870.5100	Gene mutation – bacterial reverse mutation assay Cyfluthrin	00131540 (1982) Acceptable/guideline	Negative. No increases in reverse mutations with and without activation.
870.5100	Gene mutation – bacterial reverse mutation assay Beta-cyfluthrin	41244110 (1986) Acceptable/guideline Initial assay: 20-12500 ug/plate Confirmatory assay: 500-8000 ug/plate	Negative. No increases in reverse mutations in <i>S. typhimurium</i> strains TA 1535, TA 1537, TA 98 or TA 100 with and without activation.

Appendix B, Table 4 Subchronic, Chronic and Other Toxicity Profile – Cyfluthrin and Beta-Cyfluthrin			
Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.5300	Gene mutation – <i>in vitro</i> mammalian cell gene forward mutation assay Cyfluthrin	00157796 (1985) Acceptable/guideline 3, 5, 7, 9, 10 ul/ml	Negative. Cyfluthrin did not induce forward mutations under conditions of assay
870.5300	Gene mutation – <i>in vitro</i> mammalian cell gene forward mutation assay Beta-cyfluthrin	41244112 (1989) Acceptable/guideline 50-100 ug/mL (insoluble), 20-40 ug/mL (soluble)	Negative. No mutagenic response in CHO cells HGPRT assay with and without activation.
870.5375	Cytogenetics - <i>in vitro</i> mammalian cell chromosome aberration test Beta-cyfluthrin	41205703 (1988) Acceptable/guideline 500, 1000, 5000 ug/mL	Negative. Not clastogenic in human lymphocytes.
870.5395	Cytogenetics – mammalian erythrocyte micronucleus test Beta-cyfluthrin	4124411 (1988) Acceptable/guideline 80 mg/kg	Negative. No increased frequency of micronucleated polychromatic erythrocytes in mice bone marrow cells.
870.5500	Other effects – bacterial DNA damage Cyfluthrin	00131540 (1982) Acceptable/guideline	Negative. In rec ⁻ assay, no inhibition at doses of 100- 10000 ug/disk.
870.5550	Other effects – bacterial DNA damage and repair in <i>E. coli</i> Cyfluthrin	00131538 (1981) Acceptable/guideline 62.5-1000 ug/plate	Negative. No induction of inhibition, both with and without activation.
870.5550	Other effects – unscheduled DNA synthesis in cultured rat hepatocytes Cyfluthrin	00157798 (1985) Acceptable/guideline 17, 50, 167, 500, 1667, 5000 ug/ml	Negative.
870.5550	Other effects – unscheduled DNA synthesis in mammalian cells in culture Beta-cyfluthrin	41205704 (1987) Acceptable/guideline 1.01-1010 ug/mL	Negative.

Appendix B, Table 4

Subchronic, Chronic and Other Toxicity Profile – Cyfluthrin and Beta-Cyfluthrin

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.5575	Other effects – mitotic gene conversion in <i>Saccharomyces cerevisiae</i> Cyfluthrin	00131542 (1982) Acceptable/guideline 625-10000 ug/ml	Negative.
870.5915	Other effects – <i>in vivo</i> sister chromatid exchange assay in Chinese hamster ovary cells Cyfluthrin	00157795 (1985) Acceptable/guideline Non-activated assays: 3, 5, 10, 20 ug/ml Activated assays: 125, 250, 500, 1000 ug/ml	Negative. no increase in SCE frequency in treated cells
870.6100	Delayed neurotoxicity (hen) Cyfluthrin	00156585 (1985) Supplementary 0 and 5000 mg/kg/day for 3 days	All hens died within 3 days; NTE activity was not inhibited
870.6100	Oral delayed neurotoxicity (hen) Cyfluthrin	00131543 (1981) Supplementary 10 hens: 1000 (1x), 2500 (1x), 5000 (1x) mg/kg; 30 hens: 5000 mg/kg (2x, 21 days apart); 10 hens: 5000 mg/kg (5x daily for 1 week)	In the single dose study , at 5000 mg/kg, five of the ten hens died. Moderate fiber alterations (axon fragmentation, occasional swelling and eosinophilia of the axon fragments and vacuolation of the myelin sheaths) in the sciatic nerve were observed in 2 hens. Six hens at 2500 mg/kg showed signs of excitation during the first 3 days following treatment. In the two dose study , hens showed initial signs of intoxication during the first 3 days but were normal until the second dose was administered when 4 hens died. Symptoms following the second treatment subsided; however, a second set of symptoms developed in 4/30 hens. These symptoms resembled delayed type neurotoxicity. Nerve fiber degeneration was present in the majority of the hens. The myelin sheath was distended and the myelin sheath was described as being optically void or granularly disintegrated. The axons were described as swollen or fragmented and in some areas activated or proliferated Schwann's cells were noted. The nerves also contained macrophages in which cytoplasm contained granular material. In the 5-day study , 4/10 hens died. All hens showed initial toxic responses which eventually disappeared. Behavioral disorders accompanied by drowsiness and a cramped gait were observed in 3 of the 6 survivors. Mottled kidneys and brittle livers were noted at

Appendix B, Table 4 Subchronic, Chronic and Other Toxicity Profile – Cyfluthrin and Beta-Cyfluthrin			
Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
			necropsy. Treatment-related fiber degeneration (distension or granular disintegration of the medullary sheath, swollen or fragmented axis cylinders and proliferated Schwann's cell in the sciatic nerve were reported. One hen had similar lesions in the spinal marrow.
870.6100	Oral delayed neurotoxicity (hen) Cyfluthrin	00131544 (1982) 10 hens: (5000 mg/kg, 1 x) or 20 hens: (5000 mg/kg, 2 x, 7 days apart). The first study was classified as Core supplementary - no histopathology conducted) and the second study was classified as Core minimum.	In the single dose study, the hens showed an initial weight loss but recovered. No other treatment-related effects were observed. In the two-dose study, 1 hen showed some signs of neurotoxicity on day 30. There were no microscopic lesions in the nervous system.
870.6100	Dermal delayed neurotoxicity (hen) Cyfluthrin	00131545 (1982) Minimum 5000 mg/kg (paste with cellulose powder); in the first study, 10 hens were exposed for 5 days for 23 hours/day. In the second study, 10 hens were exposed for 3 weeks, 5 days/week, 6 hours/day.	In the first study there were 2 deaths on the 3 rd and 10 th day. All other hens had symptoms (apathy and disturbed behavior) but recovered. Local irritation and weight loss were also noted. Two hens had minimal segment-like nerve fiber degeneration (sciatic nerve), but this type is often found in hens. In the second study, the hens were apathetic. These symptoms disappeared after the first week in all hens except 2, in which they persisted until the 38 th and 51 st day after the start of the treatment, respectively. Local irritation and body weight loss were also observed. No other neurologic effects were observed, including microscopic.
870.6100	Acute delayed neurotoxicity (hen) Cyfluthrin	00131510 (1983) Core minimum single 4-hour exposure or to 15 six-hour exposures over a 3-week period at concentrations of 0.285, 0.445 or 0.596 mg/L in the single dose study and 0.614 mg/L in the 3 week study	Nine of 10 hens died at 0.596 mg/L and none died in any of the lower concentrations. These had some nonspecific symptoms (behavior disturbances, sedation, eye irritancy), which disappeared after 2 days. Some initial weight loss was also noted. In the 3-week study, one hen died. Nonspecific symptoms were again observed. Nothing remarkable was noted at necropsy.
870.6100	Acute delayed neurotoxicity (hen) Cyfluthrin	00163040 (1986) Core Minimum 4300 (1x), 4300 (2x: days 1 & 21), 1500 (5 consecutive days).	4300, 1500: mortality, aggression, somnolence, cyanosis of crest. Sl. axonal degeneration of sciatic nerve in 1 hen given a single dose; sl. axonal degeneration of spinal cord in 1 hen given 2 doses. No treatment-related changes in NTE activity.

Appendix B, Table 4

Subchronic, Chronic and Other Toxicity Profile – Cyfluthrin and Beta-Cyfluthrin

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.6200a	Acute neurotoxicity (rat) Beta-cyfluthrin (≥96.9% a.i.)	44401101 (1997) Acceptable/guideline 0, 0.5, 2, 10 mg/kg In 1% Cremophor EL in deionized water	NOAEL = 2 mg/kg LOAEL = 10 mg/kg based on clinical signs, changes in FOB parameters, and decreases in motor activity.
870.6200b	Subchronic neurotoxicity (rat) Beta-cyfluthrin (≥96.5% a.i.)	44296001 (1997) Acceptable/guideline M: 0, 2.02, 7.99, 26.81 mg/kg/day F: 0, 2.34, 9.40, 30.83 mg/kg/day In corn oil, 1% by weight in diet	NOAEL = 7.99/9.40 mg/kg/day (M/F) LOAEL = 26.81/30.83 mg/kg/day (M/F) based on clinical signs, changes in FOB measurements and possibly decreased body weights, body weight gains, and food consumption
870.6300	Developmental neurotoxicity (rat) Beta-cyfluthrin (95.1-97.6% a.i.)	46054101 (2003) Acceptable/non-guideline 0, 30, 125, 200 ppm (Gestation: 0, 2.4, 11.0, 17.8 mg/kg/day)	Maternal NOAEL = 17.8 mg/kg/day Maternal LOAEL = not observed Offspring NOAEL = 11.0 mg/kg/day Offspring LOAEL = 17.8 mg/kg/day based on decreased body weight and body weight gain and decreased brain weights in females at termination.
870.7485	Metabolism and Pharmacokinetics Cyfluthrin (98% purity in 5% Cremophor EL)	00072007 (1983) Core Minimum when considered together with metabolism part of study Single oral dose: 0.5 and 10 mg/kg Single i.v. dose: 0.5 and 10 mg/kg Repeated oral dose: 0.5 mg/kg/day unlabeled for 14 days, then single dose labeled	Following oral administration, the test material was rapidly and nearly completely absorbed. Peak plasma levels of radioactivity were observed at about 2 hours after dosing. Greater than 95% of the administered radioactivity was excreted within 48 hours. Radioactivity was excreted in the urine and feces with virtually none being excreted in expired air. By 48 hours after dosing, >98% of the total retrieved radioactivity was recovered in the urine and feces. The ratio of radioactivity in urine/feces was higher in males than in females. About 50% of the total urinary radioactivity was recovered during the first 6-8 hours after dosing and about 90% within the first 24 hours. At 48 hours, only the fat tissue (renal fat) contained levels of radioactivity that clearly exceeded the overall mean body level, being 6-11X higher. Levels of radioactivity in brain were quite low, being 15-20X lower than the overall mean body level. Different dose levels (0.5 or 10 mg/kg) or pretreatment (14X) did not appreciably affect the above findings. Some sex differences, however, were observed as indicated by higher urine/feces ratios in males and slightly higher organ/tissue levels of radioactivity in females (except for fat tissue).

Appendix B, Table 4

Subchronic, Chronic and Other Toxicity Profile – Cyfluthrin and Beta-Cyfluthrin

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
			Following intravenous administration, a 2 phase plasma elimination pattern was observed with plasma half-lives of about 2.1 and 20 hours. The apparent volume of distribution (Vd) was about 17% of the total body volume, corresponding to the “readily diffusable part of the extracellular fluid”. Greater than 90% of the administered radioactivity was excreted within 48 hours. By 48 hours after dosing, about 93-94% of the total retrieved radioactivity was recovered in the urine and feces. Residual levels of radioactivity in the body and in individual organs/tissues were higher than after oral administration. In other respects, the results following intravenous dosing were quite similar to those described for oral dosing. Studies in male rats with bile fistulas indicated an enterohepatic circulation of test material.
870.7485	Metabolism and Pharmacokinetics Cyfluthrin (98% purity in 5% Cremophor EL)	00072007 (1983) Core Minimum when considered together with biokinetic part of study Single oral dose: 0.5 and 10 mg/kg Single i.v. dose: 0.5 and 10 mg/kg Repeated oral dose: 0.5 mg/kg/day unlabeled for 14 days, then single dose labeled	Excretion of radioactivity was rapid. Following oral administration, >95% of the administered radioactivity was excreted within 48 hours, and following intravenous injection, >90% within 48 hours. Most of the radioactivity was excreted in urine, the urine/fecal ratio being about 2-3X in males and about 1.6-1.8X in females following oral administration and about 2.5X in males and about 2.6X in females following intravenous injection. Parent cyfluthrin is cleaved at the ester bond and then oxidized to yield 3-phenoxy-4-fluorobenzoic acid. This intermediate is then either hydroxylated and subsequently conjugated and excreted or first bound to glycine and then hydroxylated, conjugated and excreted. Identified metabolites and parent cyfluthrin (in urine, feces and body) accounted for 65-73% of the recovered radioactivity after a single oral or intravenous dose of 0.5 mg/kg and about 82-83% of the recovered radioactivity after a single oral dose of 10 mg/kg or after 14 daily oral doses.

Appendix C Summary of Cyfluthrin/Beta-cyfluthrin Tolerances

Appendix C; Table 1 Tolerance Summary Table for Cyfluthrin/Beta-cyfluthrin				
Commodity	Established Tolerance (ppm)	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments; Correct Commodity Definition
Grass, forage, fodder and hay, group 17, forage	6.0 ¹	13.0	12	Adequate grass field trial data are available.
Grass, forage, fodder and hay, group 17, hay	8.0 ¹	40.0	50	
Alfalfa, forage	-	5.0	5.0	Adequate alfalfa field trial data are available.
Alfalfa, hay	10.0	15.0	13	
Beet, sugar, roots	-	0.09	0.10	Adequate field trial data are available
Beet, sugar, dried pulp	-	11	1.0	Maximum expected residues are 0.59 ppm based on HAFT residues of 0.049 ppm and a 12x processing factor for dried pulp.
Grain, cereal; Crop Group 15 (except Rice)	4.0	4.0	0.15	Wheat grain, barley grain, buckwheat grain, millet grain, oat grain, rye grain, triticale grain
Grain, cereal; Crop Group 15 (except Rice)	4.0	4.0	0.05	Corn, field, grain
Grain, cereal; Crop Group 15 (except Rice)	4.0	4.0	0.05	Corn, sweet, kernel plus cob with husks removed
Grain, cereal; Crop Group 15 (except Rice)	4.0	4.0	3.5	Sorghum, grain, grain
Wheat, bran	6.5	-	0.5	Stored grain uses have been revoked
Corn, field, refined oil	30.0	-	-	The field corn, grain tolerance will cover residues in corn oil
Rice, bran	6.0	-	-	Stored grain uses have been revoked
Rice, hulls	18.0	-	-	Stored grain uses have been revoked
Grain, cereal, forage, fodder and straw, Crop Group 16 (except Rice)	- ²	7.0	25	Grain, cereal, forage, fodder and hay, group 17, forage, except rice
Grain, cereal, forage, fodder and straw, Crop Group 16 (except Rice)	- ³	7.0	30	Grain, cereal, forage, fodder and hay, group 17, stover, except rice
Grain, cereal, forage, fodder and straw, Crop Group 16 (except Rice)	- ⁴	7.0	7.0	Grain, cereal, forage, fodder, and hay, group 17, straw, except rice
Grain, cereal, forage, fodder and straw, Crop Group 16 (except Rice)	- ⁵	7.0	6.0	Grain, cereal, forage, fodder and hay, group 17, bay, except rice
Wheat, forage	5.0	-	-	Crop group tolerance is being established for Forage of Grain, Cereal, except Rice (Crop Group 16)
Corn, field, forage	3.0	-	-	
Corn, sweet, forage	15	-	-	
Sorghum, grain, forage	2.0	-	-	
Corn, field, stover	6.0	-	-	Crop group tolerance is being established for Stover of Grain, Cereal, except Rice (Crop Group 16)
Corn, pop, stover	6.0	-	-	
Corn, sweet, stover	30.0	-	-	
Sorghum, grain, stover	5.0	-	-	

Appendix C; Table 1				
Tolerance Summary Table for Cyfluthrin/Beta-cyfluthrin				
Commodity	Established Tolerance (ppm)	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments; Correct Commodity Definition
Wheat, hay	6.0	-	-	Crop group tolerance is being established for Hay of Grain, Cereal, except Rice (Crop Group 16)
Wheat, straw	6.0	-	-	
Cattle, fat	10	NA	2.0	Based on the recalculated maximum dietary burdens (MDBs) for beef cattle (20.9 ppm), dairy cattle (27.1 ppm) and swine (3.21 ppm) and the residue data from the available cattle feeding study, tolerances for livestock commodities can be substantially reduced.
Cattle, meat	0.4	NA	0.10	
Cattle, meat byproducts	0.4	NA	0.10	
Goat, fat	10	NA	2.0	
Goat, meat	0.4	NA	0.05	
Goat, meat byproducts	0.4	NA	0.05	
Hog, fat	10	NA	0.5	
Hog, meat	0.4	NA	0.01	
Hog, meat byproducts	0.4	NA	0.01	
Horse, fat	10	NA	2.0	
Horse, meat	0.4	NA	0.05	
Horse, meat byproducts	0.4	NA	0.05	
Milk	1.0	NA	0.2	
Milk, fat	30	NA	5.0	
Sheep, fat	10	NA	2.0	
Sheep, meat	0.4	NA	0.05	
Sheep, meat byproducts	0.4	NA	0.05	

NA = not applicable

¹ Regionally restricted tolerances for grass grown in CA, OR, ID and WA.

² Forage tolerances are established for wheat (5.0 ppm), field corn (3.0 ppm), sweet corn (15 ppm), and sorghum (2.0 ppm)

³ Stover tolerances are established for field corn (6.0 ppm), popcorn (6.0 ppm), sweet corn (30 ppm), and sorghum (5.0 ppm)

⁴ A Straw tolerance is established for wheat (6.0 ppm)

⁵ A hay tolerance is established for wheat (6.0 ppm)



U. S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460-0001

OFFICE OF
PREVENTION, PESTICIDES,
AND TOXIC SUBSTANCES

MEMORANDUM

Date: September 28, 2007

Subject: Cyfluthrin and *Beta*-Cyfluthrin: Occupational Risk Assessment to Support the Uses on Alfalfa and Grasses and the Use of *Beta*-Cyfluthrin on Sugar Beet. Petition Nos. 6E7058 (Grasses), 6F7160 (Sugar Beet), and 7F7226 (Alfalfa).

Active Ingredients & (PC Codes): Cyfluthrin (128831) <i>beta</i> -Cyfluthrin (118831)	DP No: D339445 Other DP Nos: D339415, D340710, D340711, D340712, and D340713
EPA. Reg. Nos: 264-745, 264-784, and 264-840 Crops: Alfalfa and Grasses	Reg. No. 264-RNLA Crop: Sugar beet
Class: Insecticides	MRID: 47007811

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This occupational risk assessment includes Petition Nos. 7F7226 and 6E7058 submitted by Bayer CropScience and Interregional Research Project No. 4 (IR-4), respectively, to increase the seasonal application rates of cyfluthrin and *beta*-cyfluthrin on alfalfa and grasses, respectively and Petition No. 6F7160 submitted by Bayer CropScience to register a new use, sugar beet as a seed treatment, to the registered uses of *beta*-cyfluthrin. Bayer CropScience has also applied to register a new product formulation, Poncho Beta (EPA File Symbol: 264-RNLA) containing *beta*-cyfluthrin and clothianidin as active ingredients (AIs/ais), for the treatment of sugar beet seeds. While this document contains the occupational exposures and risk of *beta*-cyfluthrin in Poncho Beta, a separate document (S. Oonnithan, D340131, 9/28/2007) addresses the exposures and risks to clothianidin, the second AI present in the Poncho Beta formulation.

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1.0. EXECUTIVE SUMMARY

Use Patterns: The petitioners are proposing to amend the labels of cyfluthrin and *beta*-cyfluthrin to increase the maximum seasonal application rates on alfalfa and grasses, without changing the maximum single application rates. The alfalfa crop may be grown for hay or seeds and the grasses may be grown for pasture, rangeland, and/or hay and seed, and in mixed-stands with alfalfa. The submitted product formulations include two emulsifiable concentrates (ECs) and a wettable powder packed as water-soluble bags (WP/WSB). Foliar applications are made using aerial, ground boom, or chemigation equipment with a maximum 8 applications per season on alfalfa and 4 applications on grasses, all at 5 day intervals. On alfalfa and grasses, the maximum single application rates are 0.044 and 0.022 lb ai/A for cyfluthrin and *beta*-cyfluthrin, respectively. The maximum seasonal rates for cyfluthrin and *beta*-cyfluthrin on alfalfa are 0.35 and 0.176 lb ai/A respectively, and that for grasses are 0.176 and 0.089 lb ai/A, respectively

In another submission, the petitioner is proposing to add sugar beet to the uses of *beta*-cyfluthrin as a seed treatment. For this purpose, a new seed treatment liquid formulation, Poncho Beta is being registered. The sugar beet seeds may be treated with Poncho Beta (a ready-to-use liquid concentrate) at a maximum rate of 0.0043 lb ai/ lb of seed, in a commercial facility using liquid or slurry coating equipment. The treated seeds are stored until planted.

Hazard Characterization: Cyfluthrin and *beta*-cyfluthrin (an enriched isomer of cyfluthrin) have been found to have similar toxicological effects in animals and have neurotoxic type of mode of action. They have high to medium acute oral and inhalation toxicities, respectively, and low dermal and eye irritation effects. There is no potential for increased susceptibility of infants and children to cyfluthrin and therefore, Health Effects Division (HED) has concluded that no special Food Quality Protection Act (FQPA) safety factor is necessary. The toxicology database is complete, so, the uncertainty factor (UF) remains 100, which also is HED's level of concern (LOC) for the margin of exposure (MOE). For assessing the occupational risks, HED has selected the following doses for cyfluthrin and *beta*-cyfluthrin: (i) short-and intermediate-term dermal No Observed Adverse Effect Levels (NOAELs) of 2.36 mg/kg/day from a 90-day feeding study in dogs, (ii) a short-term inhalation NOAEL of 0.07 mg/kg/day from a 28-day inhalation study in rats, and (iii) an intermediate-term inhalation NOAEL of 0.02 mg/kg/day from a 13-week inhalation study in rats. A dermal absorption factor of 5% was picked to estimate the dermal exposure since the dermal end point was based on an oral study. HED has determined that the dermal and inhalation exposures can be combined to estimate the occupational risks due to the same toxicity endpoints (clinical signs of neurotoxicity and/or body weight effects). Cyfluthrin was classified as "not likely to be carcinogenic to humans."

Non-Occupational and Residential Exposures: There are several cyfluthrin containing end-use products registered for use by home owners and professional applicators for insect control in residential areas including lawns. An evaluation of such exposures has been done recently, where the risks to home owners and children were found to be below HED's LOC. With this submission, the petitioners have not proposed any new residential and/or non-occupational uses for cyfluthrin and/or *beta*-cyfluthrin.

Occupational Exposures: The proposed uses of cyfluthrin and *beta*-cyfluthrin on alfalfa and grasses are expected to result in both short- and intermediate-term exposures to mixers/loaders, applicators, and flaggers. Lacking product specific exposure data, the exposures were estimated using surrogate values from the Pesticide Handler Exposure Database (PHED) and Scientific Advisory Committee on Exposure (ExpoSAC) Policy # 9. Using the estimated exposure values and the selected toxicity doses for each exposure route and duration, MOEs were calculated for all applicable exposure scenarios of cyfluthrin and *beta*-cyfluthrin. Then the dermal and inhalation MOEs were combined to arrive at a total MOE for each duration, because the NOAELs were based on the same toxicity endpoints.

The resulting total short-term risks to mixers and loaders are of concern when they handle cyfluthrin and *beta*-cyfluthrin EC formulations for aerial applications and cyfluthrin EC formulation for chemigation, if they wear only label specified PPE. The total intermediate-term risks also are of concern while handling cyfluthrin EC for ground boom and *beta*-cyfluthrin EC for chemigation applications. These higher risks could be mitigated by adding a dust-mist respirator to the label specified PPE. For applicators and flaggers, both the total short- and intermediate-term risks are not of concern if they wear label specified PPE when applying formulations of cyfluthrin and *beta*-cyfluthrin using aerial and/or ground equipment.

The total short- and intermediate-term risks to workers who treat sugar beet seeds with Poncho Beta formulation, while wearing the label specified PPEs are not of concern. However, the total risks are of concern for both exposure durations if one worker (worker type = Multiple) handles all seed treatment steps like loading, treating, bagging, and sewing, alone on a daily basis. In actual practice, such a scenario is unlikely, due to the fact that one man operation will slow down the process considerably making it uneconomical for a commercial seed treatment facility.

Postapplication Exposures: The risks to workers who enter cyfluthrin and *beta*-cyfluthrin treated alfalfa and grass fields to do postapplication activities are not of concern when assessed for short- and intermediate-term durations. Also, the total risks to workers who plant the Poncho Beta treated sugar beet seeds are not of concern when assessed for short- and intermediate-term durations.

2.0. BACKGROUND

Cyfluthrin and *beta*-cyfluthrin (an enriched isomer of cyfluthrin) are non-systemic synthetic pyrethroid insecticides registered for the control of agricultural, household, lawn and garden and stored product pests. They are formulated into emulsifiable concentrates (ECs), aerosols, foggers, granules, ultra-low-volume sprays and wettable powders.

3.0. USE PATTERN

Alfalfa and Grasses: The label amendments for increasing the seasonal application rates of cyfluthrin and *beta*-cyfluthrin on alfalfa and grasses involved the following three products: Baythroid® 2 Emulsifiable Pyrethroid Insecticide (EPA Reg. Nos. 264-745, AI = cyfluthrin), Renounce® 20WP Insecticide (EPA Reg. No. 264-784, AI = cyfluthrin), and Baythroid® XL (EPA Reg. Nos. 264-840, AI = *beta*-cyfluthrin). The Baythroid® 2 Emulsifiable Pyrethroid Insecticide and Baythroid® XL are EC formulations and Renounce® 20WP Insecticide is a wettable powder packaged as water-soluble bags (WSB). The alfalfa crop may be grown for seed as well as cutting. The pre-gazing interval (PGI) and preharvest interval (PHI) are 7 days for both cyfluthrin and *beta*-cyfluthrin. The grasses crop includes pasture, rangeland, grasses grown for hay and seed, and in mixed-stands with alfalfa. The PGI is 0 day for pasture, rangeland, and 7 days for seed crop and mixed-stands with alfalfa. The PHI is 0 day for grass hay. Applications may be made using aerial, ground boom, or chemigation (sprinkler) equipment. ULV applications by air may also be made using 1 quart/A of vegetable oil as a carrier. The proposed label amendments on alfalfa and grasses are to increase the maximum seasonal application rates for cyfluthrin and *beta*-cyfluthrin while maintaining the same maximum rates per application (Table 1).

Table 1. Current and Proposed Application Rates for Cyfluthrin and <i>beta</i> -Cyfluthrin on Alfalfa and Grasses				
Active Ingredients and Formulations	Alfalfa		Grasses	
	Maximum Appl. Rates (lb ai/A)		Maximum Appl. Rates (lb ai/A)	
	Current ¹	Proposed	Current ²	Proposed
Cyfluthrin, Baythroid® 2 Emulsifiable Pyreth. Insecticide EPA Reg. No. 264-745	single = 0.044 # appls = ~ 5 seasonal = 0.2	single = 0.044 # appls = 8 seasonal = 0.35	single = 0.044 # appls = 3 seasonal = 0.131	single = 0.044 # appls = 4 seasonal = 0.176
Cyfluthrin, Renounce® 20WP Insecticide, EPA Reg. No. 264-784	single = 0.044 # appls = ~ 5 seasonal = 0.2	single = 0.044 # appls = 8 seasonal = 0.35	not on label ³	single = 0.044 # appls = 4 seasonal = 0.176
<i>Beta</i> -cyfluthrin, Baythroid® XL, EPA Reg. No. 264-840	single = 0.022 # appls = 4 seasonal = 0.088	single = 0.022 # appls = 8 seasonal = 0.176	single = 0.022 # appls = 3 seasonal = 0.066	single = 0.022 # appls = 4 seasonal = 0.089

1. Petition No. 7F7226 on alfalfa was submitted by Bayer CropScience and Petition No. 6E7058 on grasses was submitted by IR-4.

2. From the current labels: Reg. Nos and (approved dates) Reg. 240-745 and Reg. No. 264-784 (04/11/2007) and Reg. No. 264-840 (01/16/2007).

3. Grasses are being added as a new site

Sugar Beet: Bayer CropScience has submitted an application for registering a new formulation, Poncho Beta (EPA File Symbol: 264-RNLA) for the seed treatment of sugar beet. It contains clothianidin and *beta*-cyfluthrin at 34.3% (3.33 lb ai/gal) and 4.6%, (0.44 lb ai/gal), respectively. It is a liquid formulation used without dilution. The sugar beet seeds are to be treated in a commercial facility using liquid or slurry coating equipment at the rate of 5.07 fl. oz of product per 1 unit seed (1 unit = 100,000 seeds). At a seed weight of 4.085 lbs per 1 unit seeds, the maximum application rate amounts to 0.0043 lb *beta*-cyfluthrin and 0.032 lb clothianidin per lb of seed. [The conversion factors used are: 1 unit sugar beet seeds contain 100,000 seeds (from label), 1.0 lb of sugar beet seed contains 24,480 seeds (ExpoSAC Policy No. 15), and therefore, 1 unit seeds weigh 4.085 lbs].

4.0. HAZARD CHARACTERIZATION

Cyfluthrin insecticide has a neurotoxic mode of action. Its acute oral toxicity is high; but, it has medium to low inhalation and dermal toxicities. The acute toxicity properties of cyfluthrin technical are summarized in Table 2.

G.I. No.	Study Type	Results	Toxicity Category
870.1100	Acute Oral Toxicity (Rats)	LD ₅₀ (M) = 16.2 mg/kg	I
870.1200	Acute Dermal Toxicity (Rabbits)	LD ₅₀ (M&F) > 5000 mg/kg LD ₅₀ (M&F) > 5000 mg/kg	IV
870.1300	Acute Inhalation (Rats)	LC ₅₀ (M) > 0.735 mg/L LC ₅₀ (F) = 0.468 mg/L	II
870.2400	Primary Eye Irritation (Rabbits)	No corneal opacity; transient irritation for 3 days.	III
870.2500	Primary Dermal Irritation (Rabbits)	Non-irritating	IV
870.2600	Skin Sensitization	Not a sensitizer (Draize test)	N/A

Cyfluthrin and *beta*-cyfluthrin (an enriched isomer of cyfluthrin) have been found to have similar toxicological effects; therefore HED has combined the toxicology data bases to select the doses and endpoints used in the risk assessment of both active ingredients. The potential for increased susceptibility of infants and children to cyfluthrin was assessed and HED has concluded that no special FQPA safety factor is necessary. The toxicology database on cyfluthrin is essentially complete, therefore, the UF remains 100, which also is the LOC for the MOE. HED has determined that the dermal and inhalation exposures can be combined to estimate the occupational risks due to the same toxicity endpoints (clinical signs of neurotoxicity and/or body weight effects). Cyfluthrin was classified as "not likely to be carcinogenic to humans." The toxicological doses used for the short- and intermediate-term risk assessment are summarized in Table 3.

Table 3. Toxicological Doses Selected for Occupational Risk Assessment of Cyfluthrin and <i>beta</i> -Cyfluthrin		
Exposure Scenario	Doses	Study and Toxicological Effects
Dermal, Short-term (1-30 days) and Intermediate-term (1-6 months)	NOAEL=2.36 mg/kg/day DAF = 5 % MOE = 100 is LOC	90-Day feeding study, dog (<i>beta</i> -cyfluthrin) LOAEL = 13.9/15.4 mg/kg/day for males/females, respectively, based on decreased body weight gain, gait abnormalities, and increased incidence of vomiting.
Inhalation Short-term (1-30 days)	NOAEL=0.07 mg/kg/day IAF= 100 % MOE = 100 is LOC	28-Day inhalation study, rat (<i>beta</i> -cyfluthrin) LOAEL = 0.73 mg/kg/day based on decreases in body weight in both sexes and decreased urinary pH in males.
Inhalation Intermediate-term (1-6 Months)	NOAEL= 0.02 mg/kg/day IAF = 100 % MOE = 100 is LOC	13-Week inhalation study, rat (cyfluthrin) LOAEL= 0.16 mg/kg/day based on decreases in body weight and body weight gain in males and clinical signs in females
Cancer	Classified as "Not likely to be a carcinogen"	

1. DAF = Dermal absorption factor, IAF = Inhalation absorption factor, LOAEL = Lowest observed adverse effect level, LOC = Level of concern, MOE= Margin of exposure, NOAEL = No observed adverse effect level.

5.0. NON-OCCUPATIONAL AND RESIDENTIAL EXPOSURES

There are several cyfluthrin containing end-use product formulations registered for use by home owners and professional applicators for controlling a variety of residential insect pests including lawns. These products are packaged or applied as aerosols-, crack and crevice sprays, surface sprays and total release foggers. Use of these products results in residential and/or non-occupational exposures to cyfluthrin. An evaluation of such exposures has been done recently, where the risks to home owners and children were found to be below HED's LOC (Wang, D296251, 02/18/2005). For this petition, the registrant has not proposed any new residential and/or non-occupational uses; therefore, a new residential/non-occupational exposure assessment was not performed at this time for cyfluthrin and *beta*-cyfluthrin.

6.0. OCCUPATIONAL EXPOSURES

6.1. Use of Cyfluthrin and *beta*-Cyfluthrin on Alfalfa and Grasses

Exposure Characterization: A previous assessment on cyfluthrin reviewed the occupational risks from its use as an agricultural insecticide (S-C Wang, D296251, 02/18/2005). The proposed use pattern of cyfluthrin and *beta*-cyfluthrin on alfalfa and grasses is expected to result in both a short- (1-30 days) and an intermediate-term (1-6 months) exposure because, on alfalfa, a maximum of 8 applications per season and on grasses, a maximum of 4 applications per season are applied, both at 5 day intervals. The applicable exposure scenarios based on formulation types, application methods, and worker types for the use of both chemicals on alfalfa and grasses are summarized in Table 4.

Table 4. Short- and Intermediate-term Occupational Exposure Scenarios Applicable for the Proposed Uses of Cyfluthrin and beta-Cyfluthrin on Alfalfa and Grasses.		
No.	Exposure Scenarios	Active Ingredient
--	Mixing/Loading:	
1	liquid, open mixing/loading for aerial, fixed wing and rotary equipment	Cyfluthrin
2	liquid, open mixing/loading for ground boom equipment	Cyfluthrin
3	liquid, open mixing/loading for chemigation	Cyfluthrin
4	WP/WSB, open mixing/loading for aerial equipment	Cyfluthrin
5	WP/WSB, open mixing/loading for ground boom equipment	Cyfluthrin
6	WP/WSB, open mixing/loading for chemigation	Cyfluthrin
7	liquid, open mixing/loading for aerial equipment	beta-Cyfluthrin
8	liquid, open mixing/loading for ground boom equipment	beta-Cyfluthrin
9	liquid, open mixing/loading for chemigation	beta-Cyfluthrin
--	Applying/Flagging:	
10	liquid and WP, applying by aerial fixed wing equipment, enclosed cab	Cyfluthrin
11	liquid and WP, applying by aerial rotary equipment, enclosed cab	Cyfluthrin
12	liquid and WP, applying by ground boom equipment, open cab	Cyfluthrin
13	liquid and WP, flagging, aerial applications	Cyfluthrin
14	liquid, applying by aerial fixed wing equipment, enclosed cab	beta-Cyfluthrin
15	liquid, applying by aerial rotary equipment, enclosed cab	beta-Cyfluthrin
16	liquid, applying by ground boom equipment, open cab	beta-Cyfluthrin
17	liquid, flagging, aerial application	beta-Cyfluthrin

The labels of cyfluthrin (Baythroid® 2 Emulsifiable Pyrethroid Insecticide and Renounce® 20 WP Insecticide) and beta-cyfluthrin (Baythroid® XL) specify a basic PPE (long-sleeved shirt and long pants, socks, and shoes) plus chemical resistant gloves, and protective eye-wear (not on EPA Reg. No. 264-784 label) for handlers with a restricted entry interval of (REI) of 12-hours. For this submission, the petitioner has not submitted any product specific occupational exposure data for estimating occupational exposures; therefore, the surrogate values from PHED and ExpoSAC SOP # 9 were used to calculate the exposures to the handlers. The default values and other assumptions and parameters used for this assessment are summarized in Table 5.

Table 5. Assumptions and Parameters Used for Assessing the Exposures and Risk to Handlers From the Use of Cyfluthrin and beta-Cyfluthrin on Alfalfa and Grasses.	
Details	Values
- maximum single appl. rate on alfalfa and grasses (from Table 1)	cyfluthrin - 0.044 lb ai/A beta-cyfluthrin - 0.022 lb ai/A
- application equipment used	aerial, ground boom, and chemigation
- area (Acres) treated/day (ExpoSAC Policy SOP # 9)	aerial - 1200 ground boom - 200 chemigation - 350 flaggers - 350
- work duration/day	8 hrs
- types of exposures assessed	short- (1-30 days/year) and intermediate term
- body weight of workers	70 lb
- unit exposures	from PHED

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The following equations were used to estimate the non-cancer short- and intermediate-term exposures and risks to handlers when cyfluthrin and *beta*-cyfluthrin formulations are applied on alfalfa and grasses.

Equation No. 1. $DD = [AR * AT * DUE * DAF * CF2] / BW$

Equation No. 2. $ID = [AR * AT * IUE * CF1 * IAF * CF2] / BW$

Equation No. 3. $DMOE = DNOAEL / DD$

Equation No. 4. $IMOE = INOAEL / ID$

Equation No. 5. $Total\ MOE = 1 / [(1/DMOE) + (1/IMOE)]$ for short-term or intermediate-term exposure durations

Where,

AR	= maximum single application rate
AT	= area treated/day (acres)
BW	= body weight of workers
CF1	= conversion factor 0.001 for $\mu g/lb\ ai$ to $mg/lb\ ai$
CF2	= conversion factor 0.01 for %
DAF	= dermal absorption factor (%)
DUE	= dermal unit exposure ($mg/lb\ ai$)
DD	= dermal dose for ai handled ($mg/kg/day$)
IAF	= inhalation absorption factor (%)
ID	= inhalation dose for the ai handled ($mg/kg/day$)
IUE	= inhalation unit exposure ($\mu g/lb\ ai$)
DMOE	= dermal MOE (short- or intermediate-term)
IMOE	= inhalation MOE (short- or intermediate-term)
DNOAEL	= dermal NOAEL (short- or intermediate-term)
INOAEL	= inhalation NOAEL (short- or intermediate-term)

Chemical	Mixing/Loading Exposure Scenario #	PPE ²	Dermal Unit Exposure (mg/lb ai)	Inhalation Unit Exposure (µg/lb ai)	Dermal Dose (mg/kg/day) ³	Inhal. Dose (mg/kg/day) ⁴	Total Short-term MOE ⁵	Total Intermediate-term MOE ⁵
Cyfluthrin	1. Liquid, Open, Aerial	BL	2.9	1.2	0.109371	0.000905	17	11
"	1a. " "	BL+G+R	0.023	0.24*	0.000867	0.000181	340	110
"	2. Liquid, Open, Ground boom	BL	2.9	1.2	0.018229	0.000151	100	66
"	2a. " "	BL+G+R	2.9	0.24*	0.018229	0.000030	120	110
"	3. Liquid, Open, Chemigation	BL	2.9	1.2	0.031900	0.000264	58	37
"	3a. " "	BL+G+R	0.023	0.24*	0.000253	0.000053	1,200	360
"	4. WP/WSB, Open, Aerial	BL	0.021	0.24	0.000792	0.000181	340	110
"	5. WP/WSB, Open, Ground boom	BL	0.021	0.24	0.000132	0.000030	2,100	640
"	6. WP/WSB, Open, Chemigation	BL	0.021	0.24	0.000231	0.000053	1,200	370
Beta-cyfluthrin	7. Liquid, Open, Aerial	BL	2.9	1.2	0.054686	0.000453	34	22
"	7a. " "	BL+G+R	0.023	0.24*	0.000434	0.000091	680	210
"	8. Liquid, Open, Ground boom	BL	2.9	1.2	0.009114	0.000075	200	130
"	9. Liquid, Open, Chemigation	BL	2.9	1.2	0.015950	0.000132	120	75
"	9a. " "	BL+G+R	2.9	0.24*	0.015950	0.000026	140	120

1. Exposure scenarios, values, and assumptions are from Tables 1, 3, 4, and 5.

2. BL = baseline PPE (long-sleeve shirt, long pants, shoes with socks, and no respirator), G = Gloves, R = dust-mist respirator.

3. Dermal dose/day = Equation No. 1.

4. Inhalation dose/day = Equation No. 2

5. Total Short-term or Total Intermediate-term MOE (Equation No. 5)

*. Applied an 80% reduction factor to the inhalation unit exposures for the use of dust/mist respirator as a mitigation measure. Ref: Exposure mitigating Table (PHED).

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Table 7. Short- and Intermediate-term Occupational Risks to Applicators From the Use of Cyfluthrin and <i>beta</i> -Cyfluthrin on Alfalfa and Grasses ¹								
Chemical	Mixing/Loading/Exposure Scenario #	PPE ²	Dermal Unit Exposure (mg/lb ai)	Inhalation Unit Exp. (µg/lb ai)	Dermal Dose (mg/kg/day) ³	Inhal Dose (mg/kg/day) ⁴	Total Short-term MOE ⁵	Total Interim-term MOE ⁵
Cyfluthrin	10. Liquid & WP, Aerial, Fixed wing, Enclosed cab	BL	0.005	0.068	0.000189	0.000051	1,200	380
"	11. Liquid & WP, Aerial, Rotary, Enclosed cab	BL	0.0019	0.0018	0.000072	0.0000014	20,000	10,000
"	12. Liquid & WP, Gr. boom, Open cab	BL	0.014	0.74	0.000088	0.000093	730	210
"	13. Liquid & WP, Aerial, Flagger	BL	0.011	0.35	0.000121	0.000077	870	260
<i>Beta</i> -cyfluthrin	14. Liquid & WP, Aerial, Fixed Wing, Enclosed cab	BL	0.005	0.068	0.000094	0.000026	2,500	760
"	15. Liquid & WP, Aerial, Rotary, Enclosed cab	BL	0.0019	0.0018	0.000036	0.000001	40,000	20,000
"	16. Liquid & WP, Gr. boom, Open cab	BL	0.014	0.74	0.000044	0.000047	1,500	430
"	17. Liquid & WP, Aerial, Flagger	BL	0.011	0.35	0.000061	0.000039	1,700	510

1. Exposure scenarios, values, and assumptions are from Tables 1, 3, 4, and 5.

2. BL = baseline PPE, G = Gloves, R = dust/mist respirator; baseline PPE consists of long-sleeve shirt, long pants, shoes with socks and no respirator.

3. Dermal dose/day = Equation No. 1.

4. Inhalation dose/day = Equation No. 2

5. Total Short-term or Total Intermediate-term MOE (Equation No. 5)

Table 6 summarizes the total (dermal and inhalation) short- and intermediate-term non-cancer risks to mixers and loaders from exposures to cyfluthrin and *beta*-cyfluthrin when liquid and WP/WSB formulations are handled for aerial and ground applications on alfalfa and grasses. Using the dermal dose/day and the short- or intermediate- term dermal NOAEL (same in this case), the dermal MOEs were calculated for each exposure duration. Similarly inhalation MOEs were calculated using the inhalation dose/day and the short- or intermediate- term inhalation NOAELs. Then the dermal and inhalation MOEs for each exposure duration were combined to arrive at total MOEs for the short- and intermediate-term durations and for each of the exposure scenarios. For cyfluthrin, HED's LOC is 100; thus, a calculated MOE of <100 is of concern requiring mitigation/protection measures.

The short-term combined risk for mixers/loaders wearing only baseline PPE indicates that handling the liquid formulations (ECs) of cyfluthrin and *beta*-cyfluthrin for aerial applications resulted in risk of concern which is a reflection of the higher quantity of AIs handled/day (scenarios 1 and 7, Table 6). Handling the EC formulation of cyfluthrin for chemigation also resulted in MOE of 58 (LOC = 100). Further analysis of the individual short-term dermal and short-term inhalation MOEs (not shown here) indicated that the higher risk was from the inhalation route. Therefore, use of a dust-mist respirator was added to the baseline PPE plus gloves which provided adequate protection to the mixers and loaders (scenarios 1a, 3a, and 7a) from higher exposures. When the intermediate-term combined risks to mixers/loaders were considered, handling the EC formulation for ground boom (cyfluthrin, scenario 2) and that for chemigation (*beta*-cyfluthrin, scenario 9) applications were of concern. Here also, the inhalation exposures were found to be the contributing factor and use of a dust-mist respirator mitigated the risks. Handling the WP/WSB formulation of cyfluthrin for aerial and ground applications was not of concern for both exposure durations (scenarios 4, 5, and 6).

Table 7 summarizes the short-term combined and intermediate-term combined risks to applicators and flaggers from cyfluthrin (EC and WP/WSB formulations) and *beta*-cyfluthrin (EC) when applied using aerial and ground equipment. The results indicate that the baseline PPEs are adequate (MOEs > 260, LOC = 100) to protect the applicators flaggers when these formulations are applied on alfalfa and grasses.

The PPEs specified on the labels of all the three formulations (baseline PPE plus rubber resistant gloves) are adequate for some of the proposed mixing/loading scenarios and for applicators and flaggers. But, some other mixing/loading scenarios require in addition to the label specified PPE, use of a dust-mist respirator for adequate protection of handlers when higher quantity of AIs are handled/day, such as ECs for aerial applications.

6.2. Use of *beta*-Cyfluthrin on Sugar Beet

Exposure Characterization: The petitioner has submitted an occupational risk assessment summary (MRID 47007811) with this application. But, it was not reviewed because it did not contain any original occupational exposure data.

The proposed use pattern for sugar beet indicates, that during the seed treatment season, the workers may be treating several batches of seeds per day for several weeks resulting in short- (1-

30 days) and intermediate-term (1-6 months) exposures to the workers. The Poncho Beta is a ready-to-use (RTU) formulation, therefore, no mixing with a diluent is required prior to pouring it in the seed treatment equipment. The likely occupational exposure scenarios for the sugar beet seed treatment are the following:

- loader/applicator who transfers the formulation and treats the seeds
- bagger of treated seeds
- sewer of bags after filling with the treated seeds
- workers doing multiple activities (in a small seed treatment setup, all the operations may be performed by the same worker).

Table 8. Application Rates and Other Parameters Used for Estimating Worker Exposures to <i>beta</i> -Cyfluthrin.	
Details	Values
AIs in Poncho Beta formulation	<i>beta</i> -Cyfluthrin and Clothianidin
Conc. of <i>beta</i> -Cyfluthrin in Poncho Beta	0.44 lb ai/gal (per label)
Proposed appl. rate of Poncho Beta	5.07 fl. oz./1 Unit seed (per label)
1 Unit seed	100,000 sugar beet seeds (per label)
Conc. of <i>beta</i> -Cyfluthrin in 5.07 fl. oz	$0.0174 \text{ lb ai } [(0.44/128)*5.07] / 1 \text{ Unit seed}$
No. of sugar beet seeds per lb	24,480 ¹
Weight of 1 Unit sugar beet seeds	4.085 lbs (100,000)/24,480)
Proposed seed treatment method	commercial
Conc. of AI / lb of seed	0.0043 lb ai (0.0174/4.085)
Treating and Planting	
Quantity of seeds treated per day	52,000 ¹ (ranges 13,200 to 105,600) lbs
Area planted	80 A/day ¹
Quantity of seed planted	640 lbs/day ¹
Average work day	8 hrs
Expected frequency of exposures	short-term (1-30 days) and intermediate term (1-6 months)/year
Body weight of workers	70 lb
Unit exposures	from ExpoSAC Policy # 14 ²

1. ExpoSAC Policy No. 15, dated March 4, 2004.

2. ExpoSAC Policy No. 14, dated May 1, 2003.

Lacking product specific exposure data for estimating the occupational exposures to the workers, surrogate exposure values from HED's Standard Operating Procedures (SOPs) No. 14 and No. 15 were used and these are presented in Table 8. The formulas used to estimate the non-cancer short- and intermediate-term exposures and risks to the workers are the same that used for estimating the exposures to handlers of cyfluthrin and *beta*-cyfluthrin formulations for use on alfalfa and grasses (Section 6.1), except for the area treated per day was substituted with quantity of seeds (lbs) treated or planted per day.

The Poncho Beta label specifies the following PPEs: (i) loaders/treaters must wear long sleeved shirt and long pants, shoes with socks, chemical resistant gloves, and dust/mist respirator and (ii) baggers and sewers must wear long sleeved shirt and long pants, shoes with socks, and dust/mist respirator.

Exposure Scenarios	Worker Type	PPE ²	Qty Treated/ Planted/day (lbs)	Unit Exp. Dermal/day (mg/lb ai)	Unit Exp. Inhal/day (µg/lb ai)	Dermal Dose/day (mg/kg) ³	Inhalation Dose/day (mg/kg) ⁴	Short-term MOE ⁵	Total Interm.-term MOE ⁵
Loading/Treating	L/T	S, G	52,000	0.023	0.34	0.00365	0.00108	59	18
Loading/Treating	L/T	S, G, R	52,000	0.023	0.068 *	0.00365	0.00022	220	81
Bagging, treated seed	Bagger	S	52,000	0.0091	0.16	0.00144	0.00051	130	38
Bagging, treated seed	Bagger	S, R	52,000	0.0091	0.032 *	0.00144	0.00010	490	180
Sewing, bagged seed	Sewer	S	52,000	0.0062	0.23	0.00098	0.00073	92	27
Sewing, bagged seed	Sewer	S, R	52,000	0.0062	0.046 *	0.00098	0.00015	400	130
Doing multiple jobs	Multiple	S, G	52,000	0.0420	1.6	0.00666	0.00508	13	4
Doing multiple jobs	Multiple	S, G, R	52,000	0.0420	0.32 *	0.00666	0.00102	58	19
Handling/ Planting ⁶	Farmer, Postappl.	S, #	640	0.25	3.4	0.00049	0.00013	470	150

1. Parameters and assumptions are from Tables 3 and 8.

2. S = Single layer (long sleeve shirt and long pants) and no gloves, G = chemical resistant gloves, R = dust/mist respirator

3. Dermal dose = Equation No. 1.

4. Inhalation dose = Equation No. 2

5. Total Short-term or Total Intermediate-term MOE (Equation No. 5)

6. Postapplication exposure.

* Applied an 80% reduction factor to the inhalation unit exposure for the use of dust/mist respirator, which is a PPE requirement on the label for all seed treatment workers. Ref: Exposure Mitigating Table (PHED).

#. For handlers/planters, label specifies gloves for loading only.

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Table 9 summarizes the total (dermal and inhalation) short-term or intermediate-term non-cancer risks to workers who do the sugar beet seed treatment in a commercial facility with Poncho Beta containing *beta*-cyfluthrin. The estimated total short-term MOEs indicate that all workers, except the worker who does multiple steps of seed treatment are adequately protected, provided they all wear label specified PPE [baseline + gloves (except baggers and sewers) + dust-mist respirator]. Similarly, the total intermediate-term MOEs indicate that the worker who load/treat the sugar beet seeds are exposed to a higher risk (MOE = 81, LOC = 100) than baggers and sewers if they wear baseline PPE plus dust-mist respirator. For the worker who does multiple jobs, even with the use of a dust-mist respirator, the total short- and total intermediate-term risks are of concern (MOEs of 4 and 19, respectively). In actual practice, such a scenario is unlikely, due to the fact that one man operation will slow down the process considerably making it uneconomical for a commercial seed treatment facility.

7.0. POSTAPPLICATION EXPOSURES

7.1. Use of Cyfluthrin and *beta*-Cyfluthrin on Alfalfa and Grasses

Exposure Characterization: Postapplication dermal exposure to cyfluthrin and *beta*-cyfluthrin is likely when workers enter the treated fields under alfalfa and grasses to do irrigation, scouting, harvesting, etc. No inhalation exposure is expected during such post-treatment farm activities. Most of these postapplication operations are performed using mechanical equipment, thus reducing the worker exposure, but scouting of alfalfa and grasses grown for seeds is expected to result in result in measurable exposures.

The postapplication worker exposures were estimated using surrogate dermal transfer coefficient (TC) values from the ExpoSAC Policy No. 3.1 database. For the alfalfa crop, the highest TC was for scouting as compared with other activities. For the grass crop, lacking the crop specific TC values, representative values from a surrogate crop, alfalfa were used.

The equations and inputs used for calculating the postapplication exposures are the following:

$$\text{Equation No. 1: } DFR = AR * F * (1-D)^t * CF1 * CF2$$

$$\text{Equation No. 2: } DD = (DFR * CF3 * TC * DA * ET) / BW$$

$$\text{Equation No. 3: } MOE = NOAEL / DD$$

where:

AR	= application rate for the crop (max. lb ai/A/Application)
BW	= body weight (70 kg)
CF1	= 4.54 E+8 conversion factor for $\mu\text{g/lb AI}$
CF2	= 2.47E-8 conversion factor for Acre/cm^2
CF3	= 10E-3 conversion factor for $\text{mg}/\mu\text{g AI}$
(1-D) ^t	= fraction of residue that dissipates daily (default 10%)
DA	= dermal absorption factor (%/100)
DD _t	= dermal dose (mg/kg/day) on day 't'
DFR _t	= dislodgeable foliar residue on day 't' ($\mu\text{g}/\text{cm}^2$)
ET	= exposure time (8 hours)
F	= fraction of AI retained on foliage (default 20%)
NOAEL	= from Table 3
t	= number of days after application; (default 0 day, after the REI).
TC	= transfer coefficient

Table 10 summarizes the short- and intermediate-term dermal exposures and risks to workers who may enter cyfluthrin and *beta*-cyfluthrin treated fields of alfalfa and grasses. The short- and intermediate-term MOEs are the same for cyfluthrin because of the same toxicity endpoint for both exposure durations. The results indicate that the MOEs are of no concern (MOE = 2,800, LOC = 100) to the postapplication workers.

Table 10. Short- and Intermediate-Term Postapplication Risks to Workers Who Enter Alfalfa and Grass Fields Treated with Cyfluthrin and <i>beta</i> -Cyfluthrin.						
Crops	Chemical	Max. Single Appl. Rate (lb ai/A)	DFR $\mu\text{g}/\text{cm}^2$	Transfer Coefficient ³	Dermal Dose (mg/kg/day) ⁴	Sh. & Inter-term MOE ⁵
Alfalfa and Grass grown for seed	cyfluthrin	0.044	0.099	1500 scouting	0.00085	2,800
	<i>beta</i> -cyfluthrin	0.022	0.049	1500 scouting	0.00042	5,600

1. Among the grass crop sites (pasture, rangeland, grasses grown for hay and seed, grass mixed-stands with alfalfa), grass grown for seed is expected to have the maximum postapplication activities.
2. DFR is calculated using Equation No. 1 above.
3. Transfer coefficient (TC) is for alfalfa (surrogate crop) with medium exposure potential.
4. Dermal Dose (DD) is calculated using Equation No. 2 above.
5. Dermal MOE is calculated using Equation No. 3 above. Short- and Intermediate-term MOEs are the same because of the same NOAELs for these durations.

7.2. Use of *beta*-Cyfluthrin on Sugar Beet

Exposure Characterization: The postapplication exposure to *beta*-cyfluthrin is likely when planters transfer the treated seeds from bags to planter-hopper and/or while planting/drilling the seeds. HED has determined that the handling and planting of treated sugar beet seeds involve both dermal and inhalation exposures even if the treated seeds are not contacted directly. It is assumed that the sugar beet planting season may last for >30 days/season resulting in short- and intermediate-term exposures to planters.

The postapplication exposure to planters was estimated using surrogate values from HED's SOPs No. 14 and No. 15 and the results are presented in Table 9. The estimated total short- and intermediate-term risks are not of concern (MOEs 470 and 150 respectively) to planters of Poncho Beta treated sugar beet seeds. While the planters are seeding/planting, no direct contact with the treated seeds are expected, as the planting machinery places/drills the seed and covers it with soil, doing both steps in one operation. The treated seeds once covered with soil are protective of workers who may reenter the field soon after planting for irrigation. No other postapplication activity is performed in a freshly seeded sugar beet field. There is no restricted entry interval (REI) for treating and planting of pre-treated seeds as REI is not applicable for seed treatment operations.

8.0. CONCLUSIONS AND RECOMMENDATIONS

1. The total short-term risks to mixers/loaders are of concern when they handle (i) cyfluthrin and *beta*-cyfluthrin EC formulations for aerial applications and (ii) cyfluthrin EC formulation for chemigation, if they wear only label specified PPE. The total intermediate-term risks also are of concern while handling cyfluthrin EC for ground boom and *beta*-cyfluthrin EC for chemigation applications. These higher risks could be mitigated by adding a dust-mist respirator to the label specified PPE.
2. Both the total short- and intermediate-term risks are not of concern for applicators and flaggers wearing label specified PPE when applying formulations of cyfluthrin and *beta*-cyfluthrin on alfalfa and grasses using aerial and/or ground equipment.
3. The total short- and intermediate-term risks to workers who treat sugar beet seeds with Poncho Beta formulation, while wearing the label specified PPEs are not of concern. However, the total risks are of concern for both exposure durations if one worker handles all seed treatment steps like loading, treating, bagging, and sewing, alone on a daily basis.
4. The risks to workers who enter cyfluthrin and *beta*-cyfluthrin treated alfalfa and grass fields to do postapplication activities are not of concern when assessed for short- and intermediate-term durations.
5. The total risks to workers who plant/drill the Poncho Beta treated sugar beet seeds are not of concern when assessed for short- and intermediate-term durations.

9.0. REFERENCES

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